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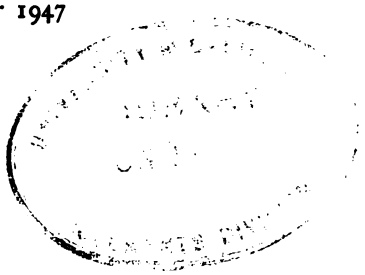
COMMITTEE OF PRIVY COUNCIL
FOR MEDICAL RESEARCH

MEDICAL RESEARCH IN WAR

REPORT OF THE MEDICAL RESEARCH COUNCIL FOR THE YEARS 1939-45

Presented by the Lord President of the Council to Parliament
by Command of His Majesty
December 1947



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COMMITTEE OF PRIVY COUNCIL FOR MEDICAL RESEARCH

(*Ex Officiis*)

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THE MINISTER OF HEALTH (*Vice-Chairman*).
THE SECRETARY OF STATE FOR SCOTLAND.
THE SECRETARY OF STATE FOR HOME AFFAIRS.
THE SECRETARY OF STATE FOR COMMONWEALTH RELATIONS.
THE SECRETARY OF STATE FOR THE COLONIES.
THE SECRETARY OF THE MEDICAL RESEARCH COUNCIL (*Secretary*).

MEDICAL RESEARCH COUNCIL

AT DATE OF REPORT

The Right Hon. Lord BALFOUR OF BURLEIGH, D.L. (*Chairman*).
Sir WILLIAM GOODENOUGH, Bart, D.L. (*Treasurer*).
Group-Captain C. A. B. WILCOCK, O.B.E., A.F.C., M.P.
Professor F. C. BARTLETT, C.B.E., F.R.S.
Professor L. J. WITTS, M.D., F.R.C.P.
Professor J. R. LEARMONTH, C.B.E., CH.M., F.R.C.S.E.
A. N. DRURY, C.B.E., M.D., F.R.S.
Professor J. C. SPENCE, M.C., M.D., F.R.C.P.
Professor P. A. BUXTON, C.M.G., M.R.C.S., F.R.S.
Sir ALEXANDER FLEMING, M.B., F.R.C.S., F.R.C.P., F.R.S.
Professor C. A. LOVATT EVANS, D.SC., F.R.C.P., F.R.S.
Professor R. A. PETERS, M.C., M.D., F.R.S.
Sir EDWARD MELLANBY, K.C.B., M.D., SC.D., F.R.C.P., F.R.S. (*Secretary*).

OTHER MEMBERS DURING PERIOD COVERED

The Right Hon. R. K. LAW, M.P.
The Right Hon. JAMES GRAY STUART, M.V.O., M.C., M.P.
Sir CHARLES G. MACANDREW, M.P.
Professor M. J. STEWART, M.B., F.R.C.P.
Professor G. E. GASK, C.M.G., D.S.O., F.R.C.S.
Professor C. R. HARINGTON, PH.D., F.R.S.
The late Professor W. W. C. TOPLEY, M.D., F.R.C.P., F.R.S.
The late Professor A. J. CLARK, M.C., M.D., F.R.C.P., F.R.S.
Professor T. R. ELLIOTT, C.B.E., D.S.O., M.D., F.R.C.P., F.R.S.
Professor E. D. ADRIAN, O.M., M.D., F.R.C.P., F.R.S.
Sir W. WILSON JAMESON, K.C.B., M.D., F.R.C.P.
Sir ERNEST ROCK CARLING, M.B., F.R.C.S. F.R.C.P.
Professor S. P. BEDSON, M.D., F.R.S.
Professor D. KEILIN, SC.D., F.R.S.
Sir HENRY H. DALE, O.M., G.B.E., M.D., F.R.C.P., F.R.S.

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REPORT OF THE COMMITTEE OF PRIVY COUNCIL FOR MEDICAL RESEARCH

FOR THE YEARS 1939–1945

TO THE KING'S MOST EXCELLENT MAJESTY IN COUNCIL

MAY IT PLEASE YOUR MAJESTY,

We, the Lords of the Committee for Medical Research of Your Majesty's Privy Council, humbly submit to Your Majesty a report of our proceedings during the six years from 1st October, 1939, to 30th September, 1945.

1. Grants-in-aid were provided by Parliament for the expenditure of the Medical Research Council in each of the financial years as follows:— 1940-41, £195,000; 1941-42, £195,000; 1942-43, £195,000; 1943-44, £215,000; 1944-45, £250,000; 1945-46, £295,000.

2. The estimates of the Medical Research Council in each of the financial years were met by our provisional allocations of funds under the following main heads:—

For administration and general purposes, including expenses of the Council, of the administrative offices and staff, and of travelling;

For the expenses of the National Institute for Medical Research at Hampstead and of the farm laboratories at Mill Hill in association with it, for the salaries of the scientific staff there and the expenses of research work done by them or by other workers temporarily attached;

For the salaries and expenses of scientific staff working elsewhere, including those in the Research Units maintained by the Council in certain hospitals, universities and other institutions, and those engaged in work under the Industrial Health Research Board;

For temporary research grants, both for personal remuneration and for expenses, to workers engaged in investigations at universities, hospitals, and other centres in the United Kingdom, and for postgraduate studentships for training in research methods;

For new buildings being erected at Mill Hill for the National Institute for Medical Research.

3. By an Order* dated 1st November, 1943, we approved amendments to the Charter incorporating the Medical Research Council (dated 1st April, 1920, and previously amended on 1st March, 1926), the amendments having been proposed by the Medical Research Council in accordance with Article 9 of the Charter. The amendments provided for an increase in the number of members of the Medical Research Council from eleven to twelve, and defined new conditions for the retirement of members.

4. By various Orders we appointed new members of the Medical Research Council or re-appointed members already serving (after the required consultation with the Medical Research Council and with the President of

* See Appendix F.

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the Royal Society in the case of members appointed or re-appointed in respect of their scientific qualifications) as follows:—

By an Order of 28th August, 1940, the Right Hon. James Gray Stuart, M.V.O., M.C., M.P., in place of Richard Kidston Law, M.P., resigned.

By an Order of 30th August, 1940, Sir William Wilson Jameson, M.D., F.R.C.P. (Dean of the London School of Hygiene and Tropical Medicine and Professor of Public Health in the University of London), in place of Matthew John Stewart, M.B., F.R.C.P. (Professor of Pathology in the University of Leeds), selected for retirement; and Edgar Douglas Adrian, M.D., F.R.C.P., F.R.S. (Professor of Physiology in the University of Cambridge) and the Right Hon. James Gray Stuart, M.V.O., M.C., M.P., reappointed after selection for retirement.

By an Order of 28th July, 1941, Ernest Rock Carling, F.R.C.S. (Senior Surgeon to the Westminster Hospital) and Sam Phillips Bedson, M.D., F.R.S. (Professor of Bacteriology in the University of London), in place of George Ernest Gask, C.M.G., D.S.O., F.R.C.S. (Emeritus Professor of Surgery in the University of London) and William Whiteman Carlton Topley, M.D., F.R.C.P., F.R.S. (late Professor of Bacteriology and Immunology in the University of London, and Secretary of the Agricultural Research Council), selected for retirement.

By an Order of 14th November, 1941, Frederic Charles Bartlett, C.B.E., F.R.S. (Professor of Experimental Psychology in the University of Cambridge), in place of Alfred Joseph Clark, M.C., M.D., F.R.C.P., F.R.S. (Professor of Materia Medica in the University of Edinburgh), deceased.

By an Order of 15th September, 1942, David Keilin, F.R.S. (Quick Professor of Biology in the University of Cambridge), Sir Henry Hallett Dale, C.B.E., M.D., F.R.C.P., P.R.S. and Sir Charles Glen MacAndrew, M.P., in place of Leslie John Witts, M.D., F.R.C.P. (Nuffield Professor of Clinical Medicine in the University of Oxford), Charles Robert Harington, Ph.D., F.R.S. (Professor of Chemical Pathology in the University of London) and the Right Hon. James Gray Stuart, M.V.O., M.C., M.P., selected for retirement.

By an Order of 30th August, 1943, Leslie John Witts, M.D., F.R.C.P. (Nuffield Professor of Clinical Medicine in the University of Oxford), in place of Thomas Renton Elliott, C.B.E., D.S.O., M.D., F.R.S. (Emeritus Professor of Medicine in the University of London and Consulting Physician to University College Hospital), selected for retirement; and Frederic Charles Bartlett, C.B.E., F.R.S. (Professor of Experimental Psychology in the University of Cambridge), reappointed after selection for retirement.

By an Order of 20th November, 1943, James Rögnvald Learmonth, Ch.M., F.R.C.S.E. (Surgeon to H.M. Household in Scotland, Professor of Surgery in the University of Edinburgh, and Surgeon-in-Ordinary, Edinburgh Royal Infirmary), appointed into the vacancy caused by the amendment to the Charter by which the number of Members of the Medical Research Council was increased from eleven to twelve.

By an Order of 15th September, 1944, Alan Nigel Drury, C.B.E., M.D., F.R.S. (Director of the Lister Institute of Preventive Medicine) and James Calvert Spence, M.C., M.D., F.R.C.P. (Professor of Child Health in the University of Durham, and Honorary Physician to the Royal Victoria Infirmary, Newcastle-upon-Tyne), in place of Edgar Douglas Adrian, O.M., M.D., F.R.C.P., F.R.S. (Professor of Physiology in the University of Cambridge) and Sir William Wilson Jameson, K.C.B., M.D., F.R.C.P. (Chief Medical Officer of the Ministry of Health), retiring in accordance with the amended provisions of the Charter; and the Right Hon. Lord Balfour of Burleigh and Sir William Macnamara Goodenough, Bart., reappointed after retirement in accordance with the said provisions.

By an Order of 1st September, 1945, Patrick Alfred Buxton, M.R.C.S., F.R.S. (Professor of Medical Entomology in the University of London) and Sir Alexander Fleming, M.B., F.R.C.S., F.R.C.P., F.R.S. (Professor of Bacteriology in the University of London), in place of Sam Phillips Bedson, M.D., F.R.S. (Professor of Bacteriology in the University of London) and Sir Ernest Rock Carling, F.R.C.S. (Consulting Surgeon to the Westminster Hospital), retiring in accordance with the amended provisions of the Charter.

5. We have received from the Medical Research Council a report, which is submitted herewith, upon the progress of their work during the six years

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from 1st October, 1939, to 30th September, 1945, corresponding approximately to the period of hostilities during the late war. This takes the place of what would normally have been the twenty-sixth to the thirty-first Annual Reports upon the research work falling now to the duty of the Medical Research Council and formerly to their predecessors, the Medical Research Committee.

6. During the war, the work of the Medical Research Council was orientated in new directions to serve the national effort, and as a result it was also greatly expanded in volume. In the first place, the attention of the Council's research workers was largely turned to problems which had assumed immediate practical importance because of the war situation: an account of this work forms the bulk of the following report. In the second place, the Council were called upon more than ever before to give scientific advice and assistance to administrative Government Departments and also to the Defence Services: a detailed statement under this head has been made to the Select Committee on Estimates of the House of Commons and has been published.* In the third place, the Council also undertook the organisation and direction of certain emergency services of a technical nature, as shown in their report.

7. To meet the needs of their wartime activities, the Medical Research Council made special arrangements for scientific liaison with equivalent organisations in different parts of the British Commonwealth. Close relations were also established with the United States of America, through the agency of British scientific representatives in Washington and of American representatives in London, and there was a regular exchange of technical information. Contacts were made, as opportunity permitted, with the Union of Soviet Socialist Republics and with other Allied countries. The normal consultation at home on research questions of common interest was maintained with the Department of Scientific and Industrial Research and the Agricultural Research Council, acting under their respective Committees of the Privy Council.

HERBERT MORRISON,

Lord President.

EDWARD MELLANBY,

Secretary to the Committee of Privy Council for Medical Research.

December, 1947.

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* Third Report from the Select Committee on Estimates, Session 1946-47: Expenditure on Research and Development. H.M.S.O., 1947. (Appendix 3, Annex B.)

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MEDICAL RESEARCH COUNCIL

HEADQUARTERS STAFF

Office :—38, Old Queen Street, Westminster, London, S.W.1.

(Temporarily, during the war, at the London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C.1)

THROUGHOUT THE WAR PERIOD

Sir EDWARD MELLANBY, K.C.B., M.D., SC.D., F.R.C.P., F.R.S. (*Secretary*).

A. LANDSBOROUGH THOMSON, C.B., O.B.E., D.SC. (*Under Secretary*).

F. H. K. GREEN, M.D., F.R.C.P. (*Assistant Secretary*).

F. J. C. HERRALD, M.B., M.R.C.P.E.

D. V. T. FAIRRIE, B.A., A.C.A. (*Finance Officer; absent on military service*, 1939–45).

J. H. DIXON (*Accountant*).

R. F. SMART (*Assistant Accountant*).

DURING PARTS OF THE WAR PERIOD

Air Vice-Marshal Sir DAVID MUNRO, K.C.B., C.I.E., M.B., F.R.C.S.E. (*Secretary, Industrial Health Research Board, till* 1942).

The late Professor W. W. C. TOPLEY, M.D., F.R.C.P., F.R.S. (1939–40).

A. N. DRURY, C.B.E., M.D., F.R.S. (1940–43).

The late D. K. M. CHALMERS, M.D., D.P.H. (1939–43, *afterwards on military service*).

R. S. F. SCHILLING, M.D., D.P.H. (*Secretary, Industrial Health Research Board*, 1942–46).

D. P. CUTHBERTSON, M.D., D.SC. (1943–45).

Mrs. J. M. FAULKNER, M.B., D.P.H. (*from* 1944).

Professor G. S. WILSON, M.D., F.R.C.P., D.P.H., K.H.P. (*Director, Public Health Laboratory Service—from* 1940).

MORE RECENTLY APPOINTED

J. G. DUNCAN, LL.B. (*Establishment Officer—from* 1945).

M. WARE, M.B., M.R.C.P. (*Publications Officer—from* 1946).

J. D. WHITTAKER, M.B.E. (*Supplies Officer—from* 1946).

Major-General Sir JOHN TAYLOR, C.I.E., D.S.O., M.D., D.P.H., I.M.S. (ret.) (*Secretary, Indian Medical Research Liaison Committee—from* 1945).

SENIOR MEMBERS OF THE CLERICAL STAFF THROUGHOUT THE WAR PERIOD

Miss V. E. Claridge (*Head Clerk*), Miss A. W. A. Nangie, M.A. (*Private Secretary to the Secretary*), Miss N. E. Bradshaw (*Administrative Assistant*), Miss D. G. Ainsworth, Miss E. M. Boyd, B.A., Miss E. Cozens, Miss G. J. Fleming, Miss M. Rees, B.Sc.

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REPORT OF THE MEDICAL RESEARCH COUNCIL FOR THE YEARS 1939-1945

To the Lords of the Committee of Privy Council for Medical Research

May it please Your Lordships,

The Medical Research Council beg leave to submit the following Report upon their proceedings during the six-year period from 1st October, 1939, to 30th September, 1945.

I

INTRODUCTION

The last preceding Report of the Council was published early in 1940, and described the work from October, 1938, to September, 1939. The present Report covers approximately the period of the second great war: it differs from its predecessors by reason both of the number of years of work reviewed and of the special nature of the duties undertaken by the Council as their contribution to the war effort.

These special duties were of two kinds. On the one hand, there was a great increase in the demands made upon the Council for advisory assistance to Government Departments and the Fighting Services in the application of the latest scientific knowledge to practical affairs. In some cases the assistance sought went far beyond advice, laying upon the Council administrative tasks of a kind which could best be performed by a scientific organisation such as they command. Many of these advisory and administrative functions were of great importance, and it has therefore been thought desirable to deal with them in this Report in considerable detail.

On the other hand, the actual research work promoted by the Council was naturally directed increasingly to the solution of problems to which especial prominence had been given by wartime needs. As would be expected, many of these problems were of an immediate kind, studied with the object of supplying quick answers to practical questions as they arose; and the more academic researches that properly hold an important place in a long-term programme were fewer. This type of *ad hoc* investigation, however, can be based only upon information and methods already available, and more complete answers often have to await the acquisition of greater fundamental knowledge. Thus, there comes a time when the research worker has to decide whether to confine his interests to giving limited answers or to delve deeper, and inevitably more slowly, to obtain a fuller grasp of the principles involved. So it is that, although war acts at first as an intense stimulus to certain branches of medical research, in the long run it tends to lose its effect as an incentive to discovery. The late war was in this way beginning to lose much of its stimulating influence on medical research when it ended. Nevertheless, as will be seen from the following pages, the harvest has been

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great; and it will bring much benefit to mankind under conditions of peace, to which many of the results obtained have also a valuable application.

War is in a sense perhaps a greater challenge to medicine than to other sciences, because the original motive which guides men and women into the field of medical research, or indeed into medical work of any kind, is a desire to reduce human suffering and to prevent untimely death. With the outbreak of war they realise that the dominant world forces are now those that involve increased suffering and are concerned to end life. In special degree, therefore, the medical worker sees all his ideals threatened with annihilation, and, quite apart from the patriotic spirit that he shares with other members of the community, he is faced by a particular challenge. Ideas of this kind were expressed in the Council's Report for 1938-39, written under the earliest impact of the war, in the following words:—

" The history of war is, in one sense, largely a race between the development of instruments of physical destruction and the advancement of medical knowledge for saving the life of wounded and sick men. The destructive power of arms will indeed have increased immensely since 1918 if it overshadows the advances in knowledge for the saving of life which modern discovery has placed at the disposal of medical men. If a strict comparison were made between what science has done to increase war mortality and what medical science has done to lessen these lethal effects, there is good reason to believe that the latter would be an easy winner. No man with any knowledge of the history of disease in relation to war would ever say that science is wholly given to the forging of instruments of destruction."

Abundant evidence will be found in the present Report to show that the advances in medical science before and during the late war have again been impressive: indeed, until the introduction of atomic weapons in the final stage, the claim that the advance in the saving of life in wartime had been at least as great as the advances in methods of destruction would not have been unreasonable. How remarkable has been the advance in what may be called medical methods of defence may be seen from the fact that in the campaign in North-Western Europe in 1944-45, if a British soldier wounded on a field of battle came into the hands of the medical service the chance of his survival was about 93 per cent., and the chance of his recovery, to a degree fitting him for a reasonably wide range of civil employment, was about 84 per cent. Compare what was said on this subject in the Council's Report for 1938-39: " Medical science has approached the point where most wounded men who escape the immediate lethal shattering of military weapons, and who receive early attention, can be expected to survive their injuries." Some of the facts which account for the high recovery rate of the wounded in the war are set out in the present Report.

The response of medical science to the challenge of war has three main objectives. First, it must be directed to maintaining the health of the armed forces and of the civilian population, particularly in the prevention of infective diseases and of malnutrition. Second, it must study methods for rapidly restoring the wounded and sick to full health. Third, an object which became very prominent in the late war, it must find the conditions required for the highest possible efficiency, safety and comfort of fighting personnel and of industrial workers in all the circumstances and tasks of war. Obviously these aims of application must also be those towards which new research under war conditions is chiefly directed.

Before dealing in turn briefly with these three main divisions of medical research in time of war, it may be well to state that, apart from acting as

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incentives to new research, the crises and emergencies of war have also been found to have an important influence in shortening the customary time-lag between the acquisition of scientific knowledge by research and its executive application to practical problems of human welfare and efficiency. Thus, the administrator suddenly faced by a question of immense magnitude and urgency, such as how to feed the nation and preserve its health during an intensive submarine and aerial blockade, or how to increase the output of munitions, turns to the appropriate research department for guidance; and the latter, often without needing to initiate any special investigation, may be able to provide an immediate answer on the basis of research in nutrition or in industrial physiology and psychology, done months or even years beforehand, the results of which had passed almost unnoticed at the time. During the recent war the Medical Research Council were able to give much expert advice to the War Cabinet and to Government Departments on the basis of knowledge acquired in previous years. Numerous occasions on which such advice was sought and given are indicated in the body of this Report.

The Maintenance of Health

The two main directions in which applications of medical science and further medical research were concentrated with the object of maintaining the health of the fighting forces and of the civil population were in increasing the control of epidemic and other infective diseases and in securing proper nutrition.

Control of Infective Diseases

Outbreaks of infective disease have always been a special menace in war and, indeed, up to the time of the opening of the present century they had often been a decisive factor. On the other hand, it is no exaggeration to say that in the recent war epidemics of infective disease were, with very few exceptions, reduced almost to strategical insignificance. It was consciousness of the part that had been played in the past by disease in wartime that made all concerned with the maintenance of health determined to apply existing knowledge to the utmost, and to extend that knowledge, for the control of such diseases as malaria, typhus, typhoid, dysentery, smallpox and yellow fever. These were all infections to which our troops were liable to be exposed in overseas theatres of war, and similar considerations in respect of the infective diseases more common in temperate climates were among the chief factors leading to the setting up of the Emergency Public Health Laboratory Service in the United Kingdom (pp. 164-181), and the Council's Committee on Tuberculosis in Wartime (p. 69). Fortunately, even before the outbreak of hostilities in 1939, methods had been discovered for preventing many of the epidemic and other infective diseases usually associated with war. In some cases, however, it was not known with certainty how effective these methods would prove in practice. For instance, as regards tetanus—that type of wound infection which killed so many soldiers in the war of 1914-18—reference to the prospects for active immunisation by toxoid injections was made in the Council's Annual Report for 1938-39, as follows:—"To what extent tetanus toxoid will ultimately replace tetanus antitoxin cannot yet be foretold. Until prophylactic inoculation by toxoid is more extensively adopted to give active immunity against tetanus, it can be regarded only as a supplement to the use of antitoxin as a means of conferring temporary passive immunity on casualties." In point of fact, war experience with tetanus toxoid showed this product to have remarkable prophylactic value; even allow-

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ing for the fact that the battle conditions of the mobile warfare of 1939-45 were less liable than the trench warfare of 1914-18 to give rise to risk of this infection, the astonishingly low incidence of the disease in the recent war among troops of the Allied armies, immunised with toxoid, bore striking witness to the efficacy of the method.

Indeed, most infective diseases thought to be controllable proved to be so in the recent war to an impressive degree. In some cases control was obtained only after new investigations had been made. This was true, for instance, of preventive inoculation by a vaccine against louse-borne typhus fever, but the method adopted as a result of researches particularly in the U.S.A. and Canada was very effective at least in reducing the severity of the disease; and this, in association with the new delousing methods provided by the use of DDT, a substance which had been introduced as an agricultural insecticide by a Swiss firm of manufacturing chemists (p. 71), made it possible to bring the serious epidemic in Naples in 1943-44 to a rapid close.

In some instances epidemic disease, rare in peacetime but occurring more frequently in war, was met with where no satisfactory control or remedy was obtained. This was the case with epidemic jaundice (infective hepatitis), which became a serious problem before the end of the war. Knowledge of its causation and prevention is still incomplete, but much new information about it has been gained in recent years. Accounts of the various researches on the subject promoted by the Council during the period of this Report will be found on pp. 66-68 and 175-176.

The greatest practical advance in the control of endemic disease during the recent war was undoubtedly made in respect of malaria, numerically still the most important disease in the world. Even in hyperendemic areas such as Burma, where it might have been expected that the disease rather than force of arms would have decided the outcome of battle, it proved possible to keep the infection in check among our troops. This great achievement depended less upon increase in fundamental knowledge during the war than upon improving the method of administration and ascertaining the optimum dosage of the drug " Atebrin ", which was introduced by the Germans as long ago as 1929 and has been made in Britain since 1940 under the non-proprietary name of mepacrine (p. 58).

Apart from the more efficient use of mepacrine—with some use also of another pre-war German drug " Plasmochin " (p. 57), now made here as pamaquin—there were two outstanding new developments in malaria prophylaxis and treatment during the recent war. The first of these was the application of the insecticide DDT, and of new insect repellents, in dealing with the mosquito vectors of the disease. The second was the preparation in the Manchester Laboratories of Imperial Chemical (Pharmaceuticals) Ltd. of a series of biguanide compounds as antimalarial agents of completely new type. One of these compounds, " Paludrine " (p. 62), seems likely to prove the most efficient antimalarial drug at present available, since it is both a true causal prophylactic in malignant tertian malaria and a partial prophylatic in benign tertian. Though developed under the stimulus of the war emergency, it was not available for field trial until nearly the end of hostilities, but its importance in the prevention and treatment of malaria in the future should be great, and it is already tending to replace mepacrine for routine prophylaxis.

One further disease of epidemic nature was encountered in the Pacific area and south-east Asia, namely, mite-borne scrub-typhus (p. 64). It was thought possible that this disease might become an important hazard of war and

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interfere with military movements and action in the Far East, and a great effort was therefore made at the National Institute for Medical Research to produce a protective vaccine. An account of the original work at the Institute, and of the arrangements subsequently made by the Ministry of Supply with the Wellcome Foundation for the manufacture of this vaccine in sufficient quantity for military needs, is given on pp. 66 and 213. Although complete arrangements had been made for the testing of the vaccine in the Far East, the end of the war prevented its large-scale trial from being completed. We are thus in the position of not yet knowing whether the fruits of this fine effort will be gathered.

Nutrition

The application of nutritional principles long advocated by the Medical Research Council, and in some cases based on discoveries by their workers, was one of the most interesting events of the war. It would be generally agreed that the impetus of modern scientific knowledge on the feeding of Service men and women throughout the war period was of great importance, and that never before had troops been so well fed. Whereas, however, it was relatively easy to apply scientific knowledge in the case of Service personnel, to whom first claim on supplies could be given, this was not so as regards the civil population. Blockade conditions were no less bad, and possibly worse, in the recent war than in that of 1914-18, but on the other hand, not only knowledge but also the organisation to deal with the situation in this country were far ahead of anything that had previously existed. Reference is made on pp. 98-99 to the valuable experiments started by Dr. (now Professor) R. A. McCance and Miss E. M. Widdowson on the outbreak of war to test the effects on a group of volunteers of diets made up of the limited number of foodstuffs which might be available under conditions of close blockade. The experimental diets chosen by these investigators were, as it proved, in general similar to the diets on which the nation as a whole had to subsist when rationing was established, so that on the basis of these results, those responsible for controlling the food situation had a good indication, in advance, of the types and quantities of available foodstuffs which were compatible with good health in young adults. To be able to make rationing and dietary plans on the basis of this knowledge must have been reassuring. In other respects the results of feeding the population during the blockade have been a triumph for those who had been engaged in nutritional research for the past thirty years. Some of the main defects of the pre-war diet of an industrialised country such as ours had often been pointed out, even before the war, and the Medical Research Council had made representation to the Government so far back as 1934 on the need for increasing the milk consumption, especially in the case of pregnant and nursing mothers and of growing children. There was good evidence that one of the most important failings of our dietary since the industrial revolution had been its poorness in calcifying qualities. This not only caused widespread bone disease, especially in children, and dental defect, but was undoubtedly responsible for much subnormal health and growth. In accordance with this view, on the outbreak of war and with the need for conserving the health of the population on a limited variety of foodstuffs, one of the main objectives of scientific advice was to secure improvement in the calcifying qualities of the diet, especially in early life. To this end the Council, on the advice of their appropriate Committees, advocated the provision of additional milk, and also of cod-liver oil and other sources of fat-soluble vitamins, to pregnant and nursing mothers, infants and children. They also recommended the addition of vitamins D and A to all makes of margarine

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and of calcium to bread. (The addition of calcium carbonate to flour followed the discovery, made immediately before the war, that phytic acid has a powerful anti-calcifying influence, and that the raising of the extraction rate of flour for bread-making from 72 per cent. to 85 per cent. greatly increased the phytic acid intake of the diet.) In these ways it was expected that the calcium intake and retention by growing children and by adults would be brought up to a level compatible with a better standard of health. This, in a nutshell, was the main scientific objective of most of the dietary changes in the war, although, of course, the increased milk consumption and the raising of the extraction rate of the flour had beneficial effects for other reasons. These changes in the nature of the dietary, together with the more equitable distribution of foods throughout all strata of the population, have probably contributed largely to the continued fall in the maternal and infant mortality rates and the stillbirth rate. Other effects, such as the large diminution in deaths due to rheumatic fever since the outbreak of war, may possibly also be related to the same kind of nutritional factors. Indeed, it is difficult to ascribe the great improvements in health standards that have developed during and since the war to causes other than the changed nutritional qualities of the diet. If, unhappily, there should be a reversal of feeding policy and a return to the faults of our pre-war dietary, it will no doubt be possible to confirm with more certainty what effects the changed nutritional qualities of the diet have had on the public health. This does not mean that the aesthetic qualities of our present diet, and in some directions its quantity, could not be greatly improved and still remain compatible with better health and physique.

Another important aspect of nutrition in which the Council have played a part is that of advising the Ministry of Food on matters where changes in or additions to the normal rations have had to be made in individual cases on account of ill health or for other special reasons. For this purpose the Food Rationing (Special Diets) Advisory Committee was set up by the Council. This Committee, a full account of whose work is given on pp. 113-127, is still active.

Restoration of the Wounded and Sick

Great as were the improvements in the treatment of wounds in the first world war, in the second these improvements were still more remarkable. The outstanding advances were the development of the blood transfusion services so that resuscitation of the injured with blood or blood products was possible even in the battle zone, the use of sulphonamide drugs and later—and much more effectively—penicillin to prevent or treat wound infection, and the more widespread recognition of the desirability of dressing wounds or burns as infrequently as possible, and then only with strict precautions to prevent extraneous infection. The substantial contributions made by workers for the Council to knowledge under all these headings are reviewed in Section II of this Report. In the main, the surgical procedures used for wounds in the late war differed little from those developed in the course of the war of 1914-18, although the establishment of mobile surgical units was of great value in facilitating early operative treatment of battle wounds; there was also a greater emphasis on skin grafting as a means of securing rapid healing, especially of burns; and there were numerous technical advances, particularly in plastic surgery and in methods of anaesthesia. From 1943 onwards, with the help of penicillin to control infection, the "two-stage" operation (p. 35) which had been introduced in 1918 for the closure of limb wounds sustained in battle, was revived with notable success.

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Additional factors in the improved recovery of the wounded and sick in the recent war, as compared with any other, were the more extensive and enlightened facilities provided for physiological and psychological rehabilitation.

The Sulphonamide Drugs

Since the first sulphonamide drug was introduced in Germany as a chemotherapeutic agent in 1935, and its life-saving value in the treatment of childbed fever was conclusively demonstrated in the following year by Dr. Leonard Colebrook and his colleagues, working for the Council in this country, an immense amount of research on the development and therapeutic possibilities of different sulphonamides has been done in Great Britain and elsewhere. During the war the value of these drugs in the treatment of various infective diseases—for example, bacillary dysentery—was more accurately defined, and they were used for the first time in the prevention and treatment of infection in battle wounds and in burns (pp. 32 and 43 *et seq.*). Many new members of the group were introduced, and unique opportunities were provided by war conditions for large-scale field trials which accelerated the assessment of their true place in the therapeutic armamentarium, especially in competition and in association with penicillin and other remedies.

Penicillin

It will be generally conceded that the greatest practical achievement of medical research in Britain during the recent war was the work of Professor (now Sir) Howard Florey and his colleagues at Oxford which led to the introduction of penicillin as a therapeutic agent, as described on pp. 78-95. The discovery by Professor (now Sir) Alexander Fleming of this substance in 1929 was of course the essential basis of this development. The urgent demands of war led to a quicker exploitation of the curative possibilities of penicillin than would have been likely under normal conditions. When Professor Florey and his colleagues had established many of the therapeutic effects of penicillin, particularly in regard to the treatment of sepsis, the development of large-scale manufacture, following a visit by Professor Florey and Dr. Heatley to the U.S.A. in 1941, was at first undertaken chiefly in America, with all the characteristic skill and drive which American manufacturers show in such work, since facilities for production work of this kind in Britain were greatly reduced in wartime, partly because of the dislocation due to air-raids (p. 81) but chiefly because most of the manufacturing resources of this country were directed to making munitions. It was a valuable piece of inter-allied collaboration which enabled the Americans to develop intensively the production side of the work, since it brought penicillin into widespread field use at a crucial period of the war and must have resulted in the saving of many thousands of lives.

Before the end of the final campaign in western Europe, there was sufficient experience of the new drug to know that by its means, combined with early and efficient surgical treatment, infection could be restricted in the great majority of battle injuries, so that it became safe to suture 90 per cent. of all wounds within a week of their infliction, with greatly improved prospects for rapid healing. It was also shown during the war that penicillin is often a life-saving drug in staphylococcal septicaemia and pneumonia and that, given in large doses, it offers fair hope of recovery even for patients with subacute bacterial endocarditis, a condition which previously had nearly always proved fatal. Of special importance under war conditions was its remarkably rapid effect in curing gonorrhoea and its very significant contribution to the problem of the treatment of syphilis.

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The Control of "Cross-Infection" in Hospitals

In the 1914-18 war attention was first drawn to the importance of hospital cross-infection of wounds, particularly by haemolytic streptococci. In sequel to these studies of many years ago, and to others made mainly in fever, obstetric and children's hospitals between the wars, some of which were referred to in previous Annual Reports of the Council, an extensive programme of research has been carried out in Britain during the last seven years on methods of preventing the principal forms of hospital cross-infection, by the use of infrequent, occlusive dressings for wounds and burns, and by adopting new methods of air purification and routines of disinfection for surgical dressing rooms, operating theatres and wards of different types. Further information about work on this subject is given in the present Report on pp. 33, 37, 195, 213-215.

Blood Transfusion and Traumatic Shock

In addition to promoting much work on problems of blood transfusion (pp. 183-195), the Council supported a wide range of other researches during the war on those physiological reactions of the body to severe injury which are generally grouped under the name of "traumatic shock". These studies, while they did not completely solve the "shock" problem, nevertheless led to results of great interest and promise; they are fully reviewed on pp. 50-56.

Factors in Human Efficiency

Service Personnel

The direction of organised research primarily to the interest of the individuals engaged in war activities was an outstanding feature of the recent war. This work became so important, and wide in scope, spreading as it did from the Royal Air Force to the Army and Royal Navy and beyond this country to the U.S.A., that a few words may be said of its origin. When, in 1937, the possibility of war with Germany became very real, the Medical Director General of the R.A.F., Air Vice-Marshal (later Air Marshal Sir Victor) Richardson approached the Secretary of the Medical Research Council with the object of setting up a Medical Research Committee in the R.A.F. The result of these discussions was to make it clear that what the R.A.F. needed most was not a research committee to study ordinary problems of medicine but one concerned with the advancement of knowledge of all personal and environmental factors conducive to improving the efficiency and safety of the flying men. It was further proposed that the committee be called the Flying Personnel Research Committee. These proposals were accepted, and the Flying Personnel Research Committee was established as a committee of the Air Ministry by the late Sir Kingsley Wood, then Secretary of State for Air, in January, 1939, with Sir Edward Mellanby, the Secretary of the Medical Research Council, as its Chairman.

On the outbreak of war, intimation was sent to the Royal Navy, Army and Royal Air Force that all the resources of the Medical Research Council were at the disposal of the Services. The R.A.F. had already become closely associated with the Medical Research Council through the establishment of the Flying Personnel Research Committee, referred to above. In 1940 the Army

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Council asked the Medical Research Council for help in investigating a number of problems relating to the protection against injury of the soldier in combat, including the design of body armour and steel helmets (p. 135). This was followed by a request that the Medical Research Council should set up a Military Personnel Research Committee, upon which both the operational and medical branches of the War Office would be represented. For two years this committee was most active and effective, as will be seen in the account given on pp. 134-147 below. Some of its sub-committees, especially the Armoured Fighting Vehicles Sub-Committee, developed greatly and were in full action even at the end of the war. Much of the research of the Military Personnel Research Committee, however, ceased after two years for reasons beyond the control of the Council. After the pioneer enterprise of the Flying Personnel Research Committee and the early success of the Military Personnel Research Committee, naval interests became subject to this same type of inquiry and, at the request of the Board of Admiralty, the Council set up the Royal Naval Personnel Research Committee, an account of the work of which is given on pp. 147-152. This Committee has been very successful and is still carrying out the same kind of work for the Navy as during wartime.

The type of research initiated and directed by the Personnel Research Committees has been concerned primarily with the individual, and more particularly with the improvement of conditions, environmental or instrumental, to make him more efficient in his task and to give him the feeling of safety and comfort. The research programmes sponsored have covered such diverse questions as the physiological problems involved in high altitude flying and in deep sea diving; the design of improved forms of clothing for aviators, for men serving in the arctic and in the tropics, and for divers in tropical seas; the ventilation of warships for tropical service and the proper training and acclimatisation of their crews; the peculiar hazards of service in submarines, including those of oxygen poisoning and escape from submerged vessels; and the design of aircraft, guns and armoured fighting vehicles in particular relation to human capabilities and needs. Moreover, the Committees have dealt with research problems of personnel selection for special forms of service, with physiological and psychological factors bearing on the optimal design of instrument panels and engine controls, and with numerous more strictly medical matters such as the choice of drugs for the prevention of sea and air sickness. A fuller account of this very important work is given in the body of the Report on pp. 131-152. The hope may be expressed that whenever in the future vast new problems involving the design and development of instruments, weapons and machinery, which have to be worked by human beings, arise, it will no longer be thought sufficient to have such matters considered only by engineers and physicists. In many cases the main limiting factor in the efficiency of the machine or weapon is the human being working it. The earlier the stage at which the human factor is considered by physiologists and psychologists in relation to machine or instrument design, the more effective will be the end result. This need for taking into consideration the human factor applies not only to machine design but to all matters where human effort is needed, whether in the military or in the civil field.

The Human Factor in Industry

The type of research just outlined for the maintenance of optimum efficiency, comfort and safety of Service personnel has long been the subject of study in industry by the Industrial Health Research Board of the Medical Research Council. Such work had its origin when the Board (then called the

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Industrial Fatigue Research Board) was established in the 1914-18 war; and, by the time of the outbreak of the recent war, a large mass of information had been collected concerning the effects of environmental and other conditions on industrial health and efficiency. Much was known about the effect of hours of labour and of such environmental factors as lighting, heating and ventilation, noise and, in certain industries, dust and toxic products, on health and output. Another aspect that had been closely studied was that of the methods of work of the operative, for instance, the optimum height of the working bench and the optimum loads to be carried, the adaptation of machines in relation to the economical expenditure of human energy, and the most efficient timing and nature of movements to be performed. Important investigations had also been made on vocational selection and on accident proneness. It is regrettable that but little was known about this work either by many industrial leaders or by the mass of workmen in the early stages of the war. Had this information been more widely appreciated it might have been possible to avoid the introduction of those excessively strenuous working conditions in the period immediately following the evacuation from Dunkirk (p. 153) which proved incompatible with a large sustained output from the factories and with a good standard of health among the work-people.

Working conditions in industry still provide a large field for study. The principles to be developed are those of suiting the job to the man, suiting the man to the job, and improving the man's performance by training, by satisfactory working conditions and by the proper incentives. Examples of the researches carried out in this field during the war years are given on pp. 153-160.

Post-war Reconstruction

Although the present Report deals only with the work of the six war years, the time-lag in publication makes it desirable to refer briefly to some of the more important developments which have already taken place during the period of post-war reconstruction. These will be described more fully in subsequent Reports dealing primarily with the years in which they properly fall.

Industrial Health

One of the most important tasks in the reconstruction of the Council's research programme has been to direct investigation towards problems of the post-war industrial effort. Not only may many lessons learned during the war be applied under conditions of peace, but methods of research then developed for immediate purposes can be adapted to new uses. Moreover, much research work that was in progress before or during the war into various aspects of industrial physiology, industrial psychology, and industrial medicine needs to be continued and extended.

Mid-way during the war, the Council established an Applied Psychology Research Unit (p. 319) in the Psychological Laboratory, University of Cambridge, as a leading centre for investigations in experimental psychology applied to practical problems of human activity. Its programme was at first naturally concerned in the main with problems relating to personnel in the Services, to which reference has already been made, but the organisation is well adapted to undertake similar problems in relation to industry. In addition, at the request of the Ministry of Works, the Council have since the war established another Unit at Birkbeck College, London, with the specific function of studying psychological and sociological problems affecting

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the building industry in particular. Other work in industrial psychology is being continued at Manchester and elsewhere. Similarly, investigations into questions of industrial physiology in relation to heating and ventilation, and to lighting, are being maintained at the London School of Hygiene and Tropical Medicine, and plans are being made for an extension of this field of physiological studies.

On the more strictly medical side of industrial health, the Council have their Department for Research in Industrial Medicine, established during the war at the London Hospital (p. 313). This has since been supplemented by an Industrial Medicine Research Unit in the Birmingham Accident Hospital (p. 267), working in close association with the Burns Research Unit already serving the Council in the same institution (p. 270).

Resuming the programme interrupted by war, the Council are making a special effort, in consultation with the Ministry of Fuel and Power, to investigate the serious problem of disability among coalminers caused by the inhalation of dust. A Pneumokoniosis Research Unit has been established at Cardiff for this purpose, and is one of the largest of the Council's external establishments.

A Toxicology Research Unit has been formed, by arrangement with the Ministry of Supply, at the Chemical Defence Experimental Station at Porton. The work will be largely concerned with health risks arising from the toxic effects of chemical substances used in industry.

In the whole of this field the Council are advised by their Industrial Health Research Board and assisted by a series of new committees appointed to deal with such special subjects as occupational physiology, occupational psychology, occupational medicine, industrial pulmonary diseases and toxicology.

Infective Diseases

The common cold remains an intractable minor ailment, causing widespread discomfort and loss of efficiency. No problem which has for so long resisted attack is likely to yield a quick solution, and only a long-term investigation into the fundamentals of the condition holds hope of any success. An obstacle to such work has always been the lack of a susceptible experimental animal, which makes it necessary to use human volunteers and therefore to make arrangements of a kind beyond the resources of the ordinary laboratory. The Council have accordingly been glad, in co-operation with the Ministry of Health, to make use for this purpose of the hutted accommodation of the hospital built near Salisbury during the war by Harvard University and subsequently presented to the British nation. A Common Cold Research Unit has been established there, as a temporary out-station of the National Institute for Medical Research. The investigations now in progress are directed towards a better understanding of the nature of the causative agent and the factors governing transmission of the infection.

Experimental work on epidemic influenza is being continued at the National Institute for Medical Research, and field studies are being undertaken in association with this. In this instance the causative agent is known to be a virus, of which the first strain to be isolated from human patients was identified by workers at the Institute in 1933, and vaccines giving some degree of protection are under trial. The question is complicated, however, by the occurrence of different strains of virus, which have to be considered separately as regards immunity, and much further knowledge is still needed of the part played by these in causing epidemics.

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The discovery in America of the antibiotic substance, streptomycin, has raised the possibility of successfully treating certain infections against which penicillin is inactive. The fact that tuberculosis is among the diseases in which streptomycin may prove useful, and notably such acute and fatal forms as tuberculous meningitis and miliary tuberculosis, is of particular importance. With the assistance of two special committees, dealing respectively with tuberculosis and non-tuberculous conditions, the Council have organised clinical trials at selected centres on as large a scale as the present supplies of the drug permit.

Medical Applications of Nuclear Physics

The access of knowledge of nuclear physics in recent years, made manifest in the atomic bomb, has created new possibilities in the application of physical methods to the study of medical and other biological problems, and the development of research on this subject has been one of the Council's most important post-war tasks. There is, in the first place, the further study of radiations as curative agents in cancer and other diseases. Secondly, there is need to determine the toxic and lethal effects of radio-active substances and to devise methods for protecting the body against these. Thirdly, the use of radio-active or stable isotopes of various chemical elements as " tracers " is of great value in the elucidation of biological function and provides new methods for the study of many fundamental problems of physiology and biochemistry. Work under the first head is being promoted by the Council in their Radiotherapeutic Research Unit at Hammersmith Hospital, and elsewhere; under the second head, in a Research Unit which they are placing, by arrangement with the Ministry of Supply, within the Atomic Energy Research Establishment at Harwell; and under the third head, in a large number of different laboratories with a central focus at the National Institute for Medical Research. In all of this work the Council are advised by their new Committee on Medical and Biological Applications of Nuclear Physics, with three sub-committees dealing with the respective branches of the subject just mentioned.

Scientific Liaison Overseas

The war created a special administrative problem of securing an exchange of information between scientific workers in the United Kingdom and those in other parts of the British Commonwealth and in Allied countries. In normal times medical research is little concerned with subjects of a secret nature, and the early publication of findings is the best method of keeping workers informed of the progress of others, wherever situated, whose investigations are following similar lines. Information regarding much of the new work published not only in Allied but also in enemy countries during the war years was, indeed, made widely available through the medium of the *Bulletin of War Medicine* (p. 201), which the Council produced from 1940 till 1946 with the co-operation of the Bureau of Hygiene and Tropical Diseases. Under war conditions, however, the publication of research results was in some cases ruled out by security considerations, and in others was rendered relatively ineffective owing to delay caused by printing difficulties and the paper shortage in Britain. It was accordingly necessary to make more definite arrangements for scientific liaison than are usually required.

In these circumstances a system was developed for the exchange and, where desirable, the dissemination of unpublished documents. This was supplemented as far as possible by personal contact. Medical and scientific

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liaison officers from the Dominions and from the United States of America, stationed in London, kept in close touch with the Council's headquarters office and appropriate research establishments. Such liaison officers also regularly attended the meetings of many of the Council's scientific committees.

In the reverse direction, the Council were indebted to the British Commonwealth Scientific Office in Washington for much action taken on their behalf in the United States and in Canada. During part of the war the Council also maintained their own liaison officer in North America, attaching him to the B.C.S.O. Professor J. H. Burn of Oxford and Professor A. D. Macdonald of Manchester successively filled this position and rendered most valuable service. Many other representatives of the Council paid shorter visits for special purposes at different times to the United States, to parts of the British Commonwealth overseas, including India, and to various foreign territories within the war zone.

In 1943 the Council were represented by one of their members Mr. (now Sir) Ernest Rock Carling, in a party of British and American surgeons visiting the U.S.S.R. In 1944 Professor (now Sir) Howard Florey and Dr. A. G. Sanders were sent to the U.S.S.R. by the Council on a short mission of scientific liaison to give information about recent developments in this country, particularly with regard to the use of penicillin, and to bring back information given to them by Russian scientists.

Although the need for the regular exchange of unpublished information has largely receded with the end of the war, the Council are continuing close official touch as well as the many informal contacts that always obtained with the Dominions and with the United States and other countries. In the case of the British Colonies a new arrangement has been made between the Council and the Colonial Office whereby a jointly appointed Colonial Medical Research Committee has, since 1945, advised both bodies. In 1945 an Indian Medical Research Liaison Committee, sitting in London, was appointed by the joint action of the Council and of the Government of India.

Deaths and Retirements

During the war period the losses by death of members and former members of the Council and of their research staff were grievous and heavy. A list is given on p. 400, but in two cases in particular the individual, while working for the Council, had rendered services to medical science so conspicuous and important as to call for mention of his achievements and history at greater length. The retirement from the Council's service of Sir Henry Dale, the first Director of the National Institute for Medical Research, also calls for special mention here.

The late Sir Patrick Laidlaw

Sir Patrick Playfair Laidlaw died suddenly of heart failure on the 20th March, 1940, at the age of fifty-nine. He had been in the Council's whole-time service for eighteen years, having been appointed to the staff of the National Institute for Medical Research in 1922 from the post of lecturer in pathology at Guy's Hospital Medical School; he became Deputy Director of the Institute in 1936. Laidlaw was one of the greatest investigators in medical research of our time, and to mention the chief discoveries with which he was associated gives but a partial idea of the wide influence he exerted in his subject. He will probably be best known for the leading part he played in virus research, especially perhaps in the isolation of the virus

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of dog distemper and in the successful production of a vaccine which has greatly reduced the incidence of that disease; in this work, he was associated with the late G. W. Dunkin. Later, with Dr. C. H. Andrewes and Dr. Wilson Smith, he followed up the distemper research by isolating the A virus of epidemic influenza. He was a born investigator of great ability and knowledge, with an exceptional command over laboratory technique in many branches of medical research. His field of interest was very extensive and, starting in blood chemistry when he had just graduated at Cambridge, he passed through a phase of experimental pharmacology and physiology and finally concentrated on problems in the sphere of pathology and bacteriology. Not only was his own work of the highest distinction, but his readiness and ability to help other research workers and to guide them out of their difficulties were also outstanding qualities.

The late Sir Thomas Lewis

Sir Thomas Lewis, who died on the 17th March, 1945, at the age of 64, joined the staff of the Medical Research Committee, as it then was, in 1916, being appointed physician on the staff of that body. He had been lecturer in cardiac pathology at University College Hospital, London, since 1911, and assistant physician there since 1912. His new appointment allowed him to give up all private practice and devote the rest of his life to medical research. It may be well to record that his was the first full-time research post in clinical medicine to be established in this country. In 1933 the Rockefeller Foundation generously endowed his directorship of the Department of Clinical Research at University College Hospital Medical School, but the Council continued to be otherwise responsible for the staffing and expenses of the Department. Being no longer technically in their service, Lewis was able to serve as a member of the Council from 1933 to 1937.

Partly by his excellent contributions to knowledge in clinical medicine, partly by his scientific writings on vascular problems, and partly by his bold advocacy of clinical science as a discipline in itself—independent of experimental research on animals—Lewis came to be regarded as a leader, nationally and internationally, in his own field. Here it is possible only to describe his researches in a general way. From 1911 to 1921 he was continuously engaged in investigating the mechanism of the heart beat, a subject to which he was led by Mackenzie's pioneer discoveries and especially by the introduction of the polygraph, and by the development of Einthoven's string galvanometer. In 1924, at the age of 43, he turned his attention almost entirely to the study of disease problems in man, and began his well known investigations on the reactions of cutaneous vessels and nerves, a subject which largely retained his interest till the end of his life. The simplicity of the apparatus and methods he used in his work on the skin and its blood vessels, and the rigid logic he constantly applied to the abundant data of his experiments, gave all Lewis's work a distinction which has seldom been surpassed in medical research. He was the recipient of the highest scientific honours and, among the many that were conferred upon him, may be mentioned the Royal Medal (1927) and the Copley Medal (1945) of the Royal Society.

Retirement of Sir Henry Dale

Sir Henry Hallett Dale retired from the service of the Council in 1942, after being a member of the staff for twenty-eight years. He was among the first

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to be appointed to the research staff in 1914, after the original Medical Research Committee was established. He was made Director of the Department of Biochemistry and Pharmacology of the National Institute for Medical Research then being formed, he and his assistants being temporarily accommodated at the Lister Institute of Preventive Medicine until the present building at Hampstead was available for occupation in 1920. In 1928 he became the first Director of the Institute as a whole, a position which he occupied for fourteen years. Since leaving the Council's staff, he has served for four years as a member of the Council.

Throughout his long period of work for the Council Dale gave most outstanding service to medical science. His achievements can be regarded as falling into three categories: in the first place, the very high quality of his own extensive investigations; secondly, the part he has played in stimulating, criticising and helping the research work of others, and especially of his colleagues in the National Institute for Medical Research; and, thirdly, the great influence he has brought to bear upon medical and, indeed, all science by his wide and public-spirited interest in scientific movements.

The field of work covered by Dale in his researches has been large and the contributions he has made to medical science are of exceptional importance. It is of interest to note that one of the subjects which he first investigated, namely, the composition and action of ergot of rye, opened up many important problems for enquiry, and much of his later work can be traced to this starting point. In this early work, he was associated with the late Professor G. Barger and the late Sir Patrick Laidlaw, the three forming a most powerful and fruitful research combination. The ergot work led Dale on the one hand into the field of the amines and the study of their physiological and pharmacological actions, and in turn by way of histamine into the study of shock and the circulatory changes associated with it, and on the other hand by way of acetylcholine into the study of the chemical transmission of the nervous impulse. It was this latter work which brought him, in association with Professor Otto Loewi, of Graz, the high distinction of the award of the Nobel Prize in Medicine for 1936.

Dale was President of the Royal Society from 1940 till 1945 and, in addition to the Nobel Prize, and the Copley Medal (1937) of the Royal Society, the many honours bestowed upon him have included the Order of Merit. On his retirement from the staff, the Council were glad to place on record their great appreciation of his magnificent service, both to their own work and to the whole field of medical science.

As the question of attracting the best brains to scientific work in the Government service is so important that various official committees have been sitting and reporting on it continuously in recent times, it is worthy of note that three such men as Laidlaw, Lewis and Dale, of the highest international fame in medical research, gave their best years, with an average period of a quarter of a century, to the service of the Medical Research Council and the predecessor Committee.

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II

WOUNDS AND INJURIES

It was natural that a large part of the Council's research programme during the war should relate to the treatment of wounds and injuries, and to the study of those dangerous sequels to injury—traumatic " shock " and the severe form of wound infection known as gas gangrene. Extensive clinical investigation of gas gangrene must, indeed, be almost limited to wartime, since, fortunately, the disease is very rarely encountered in times of peace. Important research on gas gangrene was done by British investigators in the war of 1914-18, and this was resumed almost as a consecutive story (and in some instances even by the same workers) during the war of 1939-45; even after a second phase of intensive study, however, the disease still presents many baffling features, though considerable new knowledge of its prevention and treatment has been gained.

In regard to the treatment of wounds and injuries in general, immensely important advances have been made—notably in the development of the blood transfusion services, and the production and use of blood substitutes; and in the application, first, of the sulphonamide drugs and, later, of penicillin to the prevention and cure of wound infections. In all these studies, workers on behalf of the Council have played a major part, and the committees and sub-committees set up by the Council to direct research on problems of blood transfusion, traumatic " shock ", war wounds, burns, brain injuries, nerve injuries, and the clinical uses of penicillin were accepted as advisory authorities by the Medical Departments of the Fighting Services and by the civilian Emergency Medical Services at all stages of the war. Although, chronologically, the committees on blood transfusion and on traumatic shock were the earliest to be appointed, an account of the various activities of the War Wounds Committee and its sub-committees will be given first; it will be followed, in this section, by a note on the work of an *ad hoc* committee on air-raid casualties, and by brief surveys of some of the work of the Brain Injuries Committee, the Nerve Injuries Committee and the Committee on Traumatic Shock. The work of the Penicillin Clinical Trials Committee in relation to war wounds is dealt with briefly in this section and more fully on pp. 89-90. The activities of the Council's committees on blood transfusion, which were linked closely with those of the War Wounds Committee and the Committee on Traumatic Shock, are reviewed under the heading of " Special Emergency Services " (pp. 183-195).

The Origin and Work of the War Wounds Committee, 1940–45

The War Wounds Committee (p. 413), which included representatives of the three Fighting Services, the Ministry of Health, the Department of Health for Scotland, the Ministry of Home Security and the Ministry of Pensions, was appointed by the Council in June, 1940, with the following terms of reference:—" To advise as to the application of the results of research to practice in the treatment of war wounds, and as to the need for new investigations."

The first Chairman was the late Sir Cuthbert Wallace, Bart., K.C.M.G., C.B., and the first Secretary, the late Dr. W. W. C. Topley, F.R.S. It is certain that the initiation of the Committee's extensive programme of work was due in large measure to the wisdom, energy and foresight of Sir Cuthbert Wallace and Dr. Topley. On the latter's appointment to the secretaryship of the Agricultural Research Council in the spring of 1941, he was succeeded,

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as Secretary of the Committee, by Dr. F. H. K. Green (p. 12), who had previously served as Joint Secretary. Sir Ernest Rock Carling, who had given unstinting help as Deputy Chairman during Sir Cuthbert's last illness, succeeded him as Chairman of the Committee on his death in 1944. Sir Ernest also served as Chairman of various sub-committees of the War Wounds Committee, including the Sub-Committee on Burns (p. 414), and in March, 1943, he became Chairman of the Committee on Traumatic Shock (p. 415).

The need for an authoritative committee on the treatment of war wounds became apparent during the campaign in Flanders and France in 1940, when, owing to the speed of the enemy's advance westward, large numbers of wounded had to be transferred to Britain before adequate surgical attention could be given to their injuries. The patients arriving in these convoys were distributed between military hospitals and hospitals of the civilian Emergency Medical Services, where they came under the care of many different surgeons, at a time when infection of their wounds was already of many hours' standing. A small proportion developed true gas gangrene of muscle (clostridial myositis), and a much larger number had foul gangrenous wounds of the superficial tissues, in which bubbles of gas might be present and from which gas-forming bacteria could often be isolated. The clinical differentiation of cases of the second type from true gas gangrene was (and still is) a difficult problem for the surgeon with limited war experience; and it seemed probable at that time that many patients with superficial anaerobic wound infections, causing little or no toxaemia or risk to life, were, in fact, in danger of being too drastically treated, on the assumption that the condition of their wounds represented the initial stages of gas gangrene of muscle. Moreover, as regards both gas gangrene itself and these lesser forms of anaerobic wound infection, there was an urgent need for a planned and co-ordinated scheme of combined clinical and bacteriological research to demonstrate the respective places of surgery, antitoxin and drugs in prophylaxis and treatment. Research upon the bacterial flora of wounds at different times after their infliction, and upon the use of the sulphonamides to prevent and treat streptococcal and other wound infections, also required direction and co-ordination. Work upon the local application of sulphonamides to wounds had already been undertaken in the field by Dr. Leonard Colebrook, of the Council's staff (p. 34), who had been seconded as Consultant Bacteriologist to the Army, with the rank of Colonel, at the beginning of the war. There were many other practical problems calling for similar attention, such as the treatment of burns, and the value and limitations of the " closed plaster " treatment (p. 33), which, though it subsequently fell into partial disrepute, was being extensively used for limb injuries in 1940, as a result of the high degree of success claimed for it during the Spanish Civil War. Since, however, the decisive study of any of these problems would necessarily take much time, it was agreed that an immediate function of the War Wounds Committee should be to issue detailed suggestions for the treatment of certain types of war injuries and their consequences, based on past war experience and the latest available information, making it clear that such suggestions were provisional and liable to be changed or extended as a result of further experience. Efforts should also be made to collect and collate the results of different methods of surgical treatment, and to arrange for the rapid dissemination of useful new knowledge.

Anaerobic Wound Infections

In accordance with the plan outlined above, one of the first acts of the War Wounds Committee was to prepare a short pamphlet on the diagnosis and treatment of gas gangrene. In drafting the pamphlet, the Committee had the help of the Committee of London Sector Pathologists, who also added

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a suggested scheme for the bacteriological investigation of war wounds. After approval by the Inter-Services Medical Editorial Committee (p. 199), the pamphlet was published in 1940 as " Notes on the Diagnosis and Treatment of Gas Gangrene (with a suggested scheme for the bacteriological investigation of war wounds) " (*M.R.C. War Memorandum* No. 2) and it was widely distributed by Service and other Departments to their medical officers. Subsequently, an Anaerobes Sub-Committee of the War Wounds Committee (p. 414) —including a number of surgeons and laboratory workers with special experience of the clostridial infections—was appointed under the Chairmanship of Major-General L. T. Poole, who was then the Director of Pathology, War Office; this Sub-Committee, among its many activities, shared with the main Committee the responsibility of preparing the revised edition of *M.R.C. War Memorandum* No. 2 which was published in 1943 under the title of " Notes on Gas Gangrene—Prevention: Diagnosis: Treatment." Still more recent recommendations under these headings, approved by the Sub-Committee, were incorporated in *Army Medical Department Bulletin Supplement* No. 15, 1944, and in the second edition of " The Medical Use of Sulphonamides " (*M.R.C. War Memorandum* No. 10), published in September, 1945.

Before the main War Wounds Committee was appointed, the War Office had issued a special form—Army Form I 1241—for reporting cases of gas gangrene (a somewhat similar form had been issued in respect of tetanus). This form was amplified, on the recommendation of the War Wounds Committee, so as to include a special supplement covering cases of the milder forms of anaerobic wound infection, as well as of true gas gangrene. Despite the inevitable limitations of any investigation depending on records completed by many different medical officers, under the varied and difficult conditions of active service, the information obtained from the returned copies of Army Form I 1241, analysed by members of the Anaerobes Sub-Committee, and particularly by its Secretary, Dr. Marjorie G. Macfarlane, provided useful evidence regarding the value of large doses of antitoxin given as an adjunct to surgical and drug treatment of gas gangrene. In analysing the effects of different forms of treatment, Miss Macfarlane latterly had the co-operation of Major J. D. MacLennan, R.A.M.C.; grateful acknowledgment is due also for the valuable help in checking the data which was given by Dr. E. Lewis-Faning of the Council's statistical staff.

Important experimental studies in the chemoprophylaxis and chemotherapy of anaerobic wound infections were made by Professor J. McIntosh and Dr. F. R. Selbie, at the Middlesex Hospital, on behalf of the Anaerobes Sub-Committee; these led directly to the clinical trial in the Services of sulphathiazole-proflavine (S.P.) powder, and indirectly to the more recent development and testing of the molecular sulphonamide-aminoacridine compound, " Flavazole " (Boots). Closely related studies on the effects of sulphonamides and aminoacridines applied to experimental wounds were made by Dr. F. Hawking (p. 216) and Dr. Dorothy S. Russell (p. 332), both of the Council's staff. In addition to their observations on the use of sulphonamide-aminoacridine mixtures or compounds in experimental anaerobic wound infections, Professor McIntosh and Dr. Selbie examined the value of penicillin, *p*-sulphonamidobenzylamine (introduced by the Germans as " Mesudin " or " Marfanil ") and other new chemotherapeutic agents, in the prevention and treatment of gas gangrene in laboratory animals. Work on similar problems was carried out at the National Institute for Medical Research by Dr. D. G. Evans, Dr. A. T. Fuller and Dr. J. Walker of the Council's staff (p. 216): their studies included the preparation and laboratory testing of a new sulphone drug—*p*-methylsulphonylbenzamidine (known briefly as V187)—which seems likely, on experimental grounds, to have value in the

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local treatment of anaerobic infections and of infections by sulphonamide-resistant streptococci, though it has not yet received extensive field trial for these purposes. It is of interest, also, that V187 and "Marfanil," applied locally, were found to have a chemotherapeutic effect in experimental tetanus infections in animals. In parallel with these inquiries, Dr. Evans, under the direction of Sir Percival Hartley, made some very interesting and illuminating studies of the effects of antitoxin with and without drugs, and of surgery, in the treatment of experimental gas gangrene.

Work on the mode of action of gas gangrene antitoxin, and on the bacteriological identification of clostridia causing gas gangrene, was carried out, with support from the Council, in Professor A. A. Miles's department at the Central E.M.S. Laboratory at Watford and at University College Hospital, London. This included research by Dr. E. M. Crook on the nature of the Nagler reaction, and by Miss Nancy Hayward on the development of rapid methods of identifying the three chief microbial causes of gas gangrene, using the Nagler test for *Cl.welchii* and the haemolysin test for *Cl.oedematiens* and *Cl.septicum*; the maintenance of a reference laboratory for clostridia for the use of Service and E.M.S. pathologists; and, at the request of General Poole, the training of army pathologists in anaerobic methods. Miss Hayward, with Mrs. E. M. Miles and Dr. Nuala Crowley, also investigated the bacterial flora of several hundred war wounds, and Professor and Mrs. Miles examined the causes of failure of late antitoxin therapy in experimental *Cl.welchii* intoxication. Other investigations of wound infection directed by Professor Miles during the war are noticed on pp. 266-269.

Studies of gas gangrene by Professor J. W. McLeod and Dr. J. Gordon at Leeds are mentioned on pp. 393-394.

In preparation for the invasion of Normandy in 1944, the War Wounds Committee, the Anaerobes Sub-Committee and the Penicillin Clinical Trials Committee (p. 87) co-operated with the Medical Departments of the Fighting Services, and with the Emergency Medical Services, in arranging a large-scale investigation of the value of penicillin and other drugs in the prevention and treatment of wound infection in casualties evacuated to Great Britain. Further reference to these studies and their practical outcome is made on pp. 35 and 89. Various clinical, pathological and biochemical investigations of gas gangrene by expert teams were arranged at the same time; they included observations by Professor E. J. King, of the British Postgraduate Medical School, London, and other workers, on the acidosis occurring in the disease. As part of the same comprehensive research scheme, Dr. R. G. Macfarlane, of the Radcliffe Infirmary, Oxford, was seconded to the R.A.M.C., with the rank of Major, to co-operate with Major J. D. MacLennan in studies of certain aspects of the toxaemia of gas gangrene; he continued this work subsequently with a grant from the Council at Oxford.

One of the main objectives of the Anaerobes Sub-Committee, on its appointment, was the production of toxoids for the active immunisation of troops against the more important clostridia of gas gangrene. A powerful stimulus to this work was the remarkable success achieved in the Allied Armies during the recent war, by the use of toxoid immunisation against tetanus. Considerable progress was made in the preparation and purification of gas gangrene toxoids suitable for clinical use, and trials in laboratory animals showed that active immunisation with these toxoids gave a high degree of protection against infection. It was hoped that it might be possible to produce a combined toxoid which would protect both against tetanus and against gas gangrene due to *Cl.welchii* or *Cl.oedematiens*. Owing to technical difficulties in the large-scale production of an active toxoid of *Cl.welchii*, that hope had not been

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realised by the end of the war, though encouraging results had been obtained in small-scale trials in groups of soldiers and civilian volunteers. Information of much scientific interest about the immunising effects of clostridial toxoids was obtained during these studies, and it is hoped to publish an account of them as part of a monograph on anaerobic wound infections. Among those who took part in the preliminary researches were: Dr. B. C. J. G. Knight, Dr. Marjorie Macfarlane and Dr. Muriel Robertson, of the staff of the Lister Institute of Preventive Medicine, Mr. J. Keppie, Dr. W. E. van Heyningen, who for a time had personal and expenses grants from the Council at Cambridge, and Dr. D. Herbert, who at that time had an expenses grant at Cambridge. More detailed reference to the studies at Cambridge, with the names of other collaborators, will be found in the report of Dr. Marjory Stephenson, of the Council's staff (p. 308). Dr. Knight and Dr. van Heyningen later joined the staff of the Wellcome Physiological Research Laboratories at Beckenham, where work on large-scale toxoid production was carried out, with the collaboration of Mr. Glenny and Dr. Parish in the immunisation trials.

The Prophylaxis and Treatment of Wound Infections in general

Brief reference has been made above to work carried out for the Anaerobes Sub-Committee on the prevention and treatment of gas gangrene by means of penicillin and other drugs, used as adjuncts to surgical operations and the administration of antitoxin. Gas gangrene, however, is, fortunately, one of the rarest forms of wound infection: it is important only because of its severity, and the danger it involves to life or limb; it is, moreover, particularly difficult to treat successfully with drugs, since it usually develops in lacerated muscle deprived of its blood supply—which means that medicaments injected or absorbed into the blood-stream may not be able to reach the affected tissues. The study of the prevention and treatment of other types of wound infection during the recent war was not only much wider in its scope, but was attended by a very much higher degree of clinical success. It is proposed, first of all, to review very briefly the development of wound treatment throughout the war, as exemplified particularly by the treatment of limb wounds in the British Army, relating this to work directly sponsored by the Council and the War Wounds Committee; thereafter an attempt will be made to summarise current opinions of the uses and limitations of the sulphonamides and penicillin in the prevention and treatment of wound infection.

A lesson learnt in previous wars, which nothing in the experience of 1939-45 has contradicted, is that the most effective way of preventing infection by the bacteria introduced into wounds at the time of injury is by early and adequate surgical operation; this should generally include the opening up of " dead spaces " in the tissues, the removal of contaminated foreign bodies, the trimming of the walls of the wound cavity (to provide a surface of healthy tissues), the relief of fascial tension and the provision of free drainage, with the conservation of as much skin and viable bone as possible. The operation commonly used for this purpose has been described variously as " wound excision ", " wound revision ", " *épluchage* " and " *débridement* ", though, as indicated in a note by Sir C. Max Page in the *Bulletin of War Medicine* (1945, **5**, 422), the last of these terms should properly be used only in its specialised original sense, namely, to indicate relief of tension in the tissues by means of incision, and the removal of foreign bodies. For the more comprehensive operative procedure summarised above, the terms " wound excision " or " wound revision " are considered preferable; an account of the technique of wound excision, drafted by Surgeon Rear-Admiral Sir Gordon Gordon-Taylor on behalf of the War Wounds Committee,

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was published in *M.R.C. War Memorandum* No. 2 and in the *Bulletin of War Medicine* (1943, **3**, 535). It is clear from world-wide experience in the recent war that the chemoprophylaxis of wound infection by the administration of sulphonamides, penicillin or other drugs is at best of secondary importance to early surgical treatment, and the latter should never be unnecessarily delayed because such drugs have been used; nevertheless, as will be indicated later, penicillin has proved of the very highest value in restraining the development of wound infection in circumstances where early surgical treatment was impracticable.

A very significant point in wound treatment, brought out by research in the recent war in continuation of studies begun in the war of 1914-18, was the risk of " hospital cross-infection " of the open wound or burn, and the need to take strict measures to prevent it. Although, as already indicated, bacteria causing wound infection may be introduced into the body at the time of injury, research, in which workers for the Council took a leading part, has shown that the haemolytic streptococci responsible for some of the commoner types of severe wound sepsis much more often reach the exposed tissues later, when the wounds are being dressed after the primary operation. These organisms are among those carried in the throats and noses of perfectly normal people, and they are easily conveyed to the surface of a wound by the contact of soiled fingers, instruments or dressings, by infected droplets from the mouths and noses of those nearby when dressings are removed, and by the dust in the air of a ward. Work on this question of " hospital cross-infection," and on special measures to prevent it, is noticed later in this Report (pp. 37 and 195). While much new knowledge of these problems was gained during the war, it had been realised from earlier experience that, to minimise the risk of added infections, wounds should be kept securely covered after the primary operation and be dressed as infrequently as possible; the importance of immobilisation in the treatment of limb injuries was also appreciated. Since primary suture of battle wounds, immediately after the initial operation, is rarely safe, alternative methods had to be found to protect the wound from environmental contamination.

The method favoured for this purpose during the campaign in France and Flanders in 1940 was the " closed plaster " treatment, as used during the Civil War in Spain, though its history is of much earlier origin. Immediately after the operation of wound excision, the injured extremity (with or without a compound fracture) was enclosed in a skin-tight plaster-of-Paris splint, for the patient's transport to a base hospital: the plaster was left undisturbed for periods up to several weeks, unless there were clinical indications for removing or changing it earlier. This method was, on the whole, well suited to the conditions of that particular campaign, with its lengthy and difficult lines of evacuation; it had the advantages of protecting the wound from air-borne contamination, of securing good immobilisation, and of discouraging redressing, but it also had serious disadvantages. The first of these was that, unless the plaster was very carefully applied, and the patient carefully observed thereafter, there was a risk of interference with the blood supply to the limb, and of the development of gas gangrene, or other dangerous infection, inside the casing; this risk proved sufficiently great to lead subsequently to a prohibition of the use of closed unpadded plasters for the treatment of British wounded in the field. A less serious but important practical disadvantage of the closed plaster treatment, as widely used in 1940, was the offensive smell commonly associated with the soaking of wound discharge through the plaster casing. A method of overcoming this, by enclosing the limb and plaster in a bag made of carbon-impregnated cloth, was devised by Professor H. J. Seddon, Professor (now Sir) Howard Florey and colleagues at Oxford, in co-operation with the Chemical Defence Research Department (Ministry of Supply) and the

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Wool Industries Research Association. Large-scale clinical tests organised by the War Wounds Committee confirmed the value of this procedure, and thereafter it was extensively used in Service and civilian hospitals.

The action of the sulphonamide drugs against streptococcal and other infections had been established well before the war, and it was logical to try these drugs for the control of wound infections. As already indicated on p. 29, Dr. Leonard Colebrook, of the Council's staff, had been appointed Consultant Bacteriologist to the Army in 1939, to direct investigations on these lines. Treatment with sulphonamides by the mouth was at first contemplated, but reports by Jensen and his colleagues in America (on compound fractures treated in civil practice), and the experiments of Legroux at the Institût Pasteur in Paris, soon made it clear that the local application of the drugs was also likely to have an important effect. With the generous help of Professor Legroux and Dr. Tréfouël, of the Institût Pasteur, who had already initiated an active programme of local treatment in the French Armies defending the Maginot Line, plans were quickly made for a similar trial in units of the British Army—and for the follow-up of wounded men so treated. The clinical studies of Dr. (then Colonel) Colebrook and others were supplemented by laboratory experiments in which Dr. F. Hawking, of the Council's staff (pp. 203 and 216) had a large share. Conditions in the Campaign of 1940 were unfavourable to the routine field application of a new form of treatment, and only a small proportion of the casualties evacuated to Britain in that year had received sulphonamide prophylaxis. From the point of view of general military surgery, therefore, that period has been described as the " pre-sulphonamide era ", it was a period " when local sepsis was rife and spreading or generalised infections relatively common ".

Further attempts to assess the value of sulphonamides in the prevention and treatment of infection in wounds treated in " closed plasters " or otherwise were made subsequently in Britain, particularly during the period of intensive air-raids in 1940-41. These observations on air-raid casualties suffered scientifically from the disadvantage that it naturally was not considered ethically justifiable to withhold from such patients any method of treatment which might improve their chances of recovery; there was thus great difficulty in securing adequate control groups. Nevertheless, the impression was gained in these studies that sulphonamides given by mouth and/or applied locally were of value at least in preventing the systemic spread of local wound infections, and that impression has been borne out by more recent experience in the field. One carefully controlled small-scale study, made for the War Wounds Committee by Professor A. D. Gardner and his colleagues at Oxford, showed that a single local application of sulphanilamide to severe limb injuries at the time of early surgical excision, and before they were enclosed in " complete plasters ", caused a prolonged selective reduction of the wound flora, but had no demonstrable clinical effect upon the progress of the cases; nevertheless, haemolytic streptococci, if present at the time of operation, were usually eliminated by the drug.

Meanwhile, it had been established by Colonel Colebrook and Major A. E. Francis, R.A.M.C., working in Sir Harold Gillies's Plastic Surgery Unit at Basingstoke, that the local application of sulphanilamide powder or cream to *superficial* wounds infected with haemolytic streptococci usually resulted in the elimination of those microbes within five or six days; that discovery made a landmark in the treatment of infected wounds. In the course of these studies, Colonel Colebrook and Major Francis encountered various strains of haemolytic streptococci which were insusceptible to the action of sulphonamides (" resistant " strains); these occurred in patients receiving sulphonamide treatment, and subsequent work left little doubt that they had developed by adaptation of originally susceptible strains; during the same studies, Colonel

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Colebrook and other colleagues observed that another biological variant of the group A haemolytic streptococcus, namely a non-haemolytic form, was sometimes responsible for septic infections and might easily be missed on account of its failure to haemolyse blood in the ordinary laboratory media. Dr. Colebrook's work on burns, after his release from the Army, is noticed on pp. 46 and 270.

At various times from 1940 onwards, the War Wounds Committee reviewed the existing state of knowledge of the uses and limitations of sulphonamides in wound treatment, and drafted instructions for the guidance of the Service Departments. The latest recommendations approved by the Committee under this heading are incorporated in the second (1945) edition of *M.R.C. War Memorandum* No. 10 (p. 77).

In the period of the North African campaigns, sulphonamides were extensively used in the treatment of the wounded, and some notable modifications in the early surgical treatment of limb injuries had by then been adopted: excision and " closed plaster " had been replaced by excision with drainage, followed by immobilisation in padded and split plaster casts, such as the " Tobruk splint." In this " sulphonamide era " of wound treatment, local sepsis continued to be common, but severe generalised infections became much more rare, even under unfavourable conditions of evacuation.

Early in 1943, a team of workers was sent by the War Office to North Africa, to investigate the practicability of using penicillin for the prevention and control of wound infections in the field. This very important pioneer work, in which Sir Howard Florey and Brigadier (now Sir) Hugh Cairns took a leading part, is described in greater detail on pp. 85-86. In its subsequent developments, in Italy and elsewhere, it has led to a revolution in wound treatment. Since penicillin has become freely available, it has tended more and more to replace the sulphonamides for the prophylaxis and treatment of wound infections.

During the campaign in Italy which began in 1943, a fundamental change in the surgical treatment of limb injuries became practicable, owing to the relatively short lines of evacuation, and the protection against serious infection given particularly by the use of penicillin. This was a reversion to the " two-stage " operation of wound closure, which had been used with considerable success in 1918, though, of course, without the helpful accompaniment of chemotherapy. In this procedure, the primary excision of the wound, and its closure (usually) three to five days later, were regarded as the two stages of one process. The results of this method of treating wounds were extremely satisfactory, and it was used increasingly during the final campaigns in Western Europe and in the Far East.

Reference has been made above (p. 31) to the arrangements made before ' D-day," in 1944, for the treatment of casualties with penicillin during the period of their evacuation to hospitals in Great Britain. While the inevitable absence of comparable control series of untreated patients made it difficult to state with certainty that penicillin was responsible for the remarkably low incidence of severe infection in the wounds of the men so treated, few of those who had to deal with them felt any doubts on the subject. As a result of the co-operative scheme of investigation then organised, a number of interesting reports by individual investigators, on the use of penicillin in different types of wound infection, was published in the medical press. A pamphlet entitled " The Use of Penicillin in Treating War Wounds," based on previous field experience, had been published earlier in 1944, as *M.R.C. War Memorandum* No. 12; this had been prepared by the Penicillin Clinical Trials Committee (p. 89), upon which several members of the War Wounds Committee served, so as to secure adequate liaison between the two bodies.

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Among the administrative arrangements made in preparation for " D-day," was the adoption of a special yellow label, to be tied to patients with wounds of such severity that prophylaxis by repeated intramuscular injections of penicillin was deemed essential during the stages of their evacuation; the label served to remind medical officers of the need to give the injections at regular intervals, recorded the dosage of the drug given to the patients, and, together with other records, was used subsequently in analyses of the effects of prophylaxis or treatment with penicillin in wounds of different types. These analyses were made by the Army Statistical Department, with the co-operation, from the clinical aspect, of Major A. H. Hunt, R.A.M.C., who for a time had a grant from the Council for the purpose.

The results of penicillin prophylaxis in the patients evacuated to Britain from Normandy were so encouraging that the use of penicillin systemically (and sometimes locally as well) was adopted to an increasing extent for the prevention of wound infection in the British Liberation Army, after facilities for early primary operation, and the " two-stage " wound closure, had been established on the Continent. The remarkably good results obtained in the B.L.A. with penicillin in wounds and other conditions, are described in the book " Penicillin Therapy and Control " published by 21 Army Group in May, 1945. In the middle and later phases of this campaign, the organisation of forward surgery, penicillin therapy, evacuation, and base surgery was co-ordinated to allow the closure of 90 per cent. of wounds within a week of their infliction; generalised infections from wounds became " the greatest rarity " and local infections were reduced to " quite small proportions "; statistics show that the wounded man in 21 Army Group had more than a nine to one chance of living once he reached surgical aid—a record of success in wound treatment never before achieved in military surgery, and one for which penicillin must undoubtedly be given a large share of the credit.

It is now possible to survey the evidence made available from various sources during the war years on the respective values of the sulphonamide drugs and penicillin in the prevention and treatment of wound infection. The following is believed to represent a fair summary of current views:—

(1) Sulphonamide drugs, applied locally or given systematically (or both), are of only limited value in restraining the development of local infection in wounds, but are of definite value in preventing the systemic spread of streptococcal infection from a local focus such as a wound or burn. Both penicillin and the sulphonamides are effective in treating such systemic streptococcal infections on the rare occasions when these occur.

(2) It has been shown conclusively by Colebrook and others (p. 34) that the local use of sulphonamides will control infection by susceptible bacteria in superficial wounds, either in the early stages or in the stage of granulation; it is in deeper wounds, and wounds with recesses, that these drugs, however administered, often fail to prevent or cure a local infection even by bacteria against which they are active in the laboratory. The sulphonamides, used locally, are of value in preparing superficial wounds or burns for early skin-grafting, and penicillin, used locally, systemically or both, is still better for this purpose; penicillin appears to be much more effective than the sulphonamides in making deep wounds safe for delayed primary, or secondary, closure (the second stage of the " two-stage " operation).

(3) Penicillin has some outstanding advantages over the sulphonamides: it is effective against a wider range of gram-positive bacteria, including most strains of staphylococci, against which the action of even the most potent sulphonamides is relatively small; unlike the ordinary sulphonamides, it is

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not antagonised by the presence of pus; it can be given systemically in large doses—and in repeated courses—without serious danger of toxic effects, and it can be injected locally, with much less risk than the sulphonamides, into body cavities such as joints, the pleura or the spinal theca. Among its practical disadvantages, as compared with the sulphonamides, is the fact that it cannot, economically, be given by the mouth and its systemic use necessitates repeated or continuous injections under expert supervision. The combined use of penicillin injections and of sulphonamides by the mouth has not been shown to give better prophylactic results against wound infection than the use of penicillin injections alone. Moreover, the giving of the less soluble members of the sulphonamide group of drugs carries a risk of renal damage, especially in dehydrated patients.

(4) Neither penicillin nor sulphonamide prophylaxis is a substitute for early and efficient primary surgical treatment of the wounded, but penicillin is a very valuable adjunct to surgery, which assists both the surgeon's task and the patient's chances.

(5) Neither penicillin nor the sulphonamides will prevent the occasional development of gas gangrene in limbs deprived by injury of their blood supply (p. 32) and containing damaged and ischaemic muscle tissue. In the treatment of gas gangrene, the value of penicillin and the sulphonamides, as adjuncts to surgery and antitoxin, has yet to be definitely decided. There is suggestive, but not conclusive, clinical evidence that penicillin gives better results than the sulphonamides in this disease.

(6) Neither penicillin nor sulphonamide therapy is effective against the gram-negative bacteria which may infect wounds or burns at a relatively late stage (the stage of sloughing). For these cases, alternative methods of treatment are necessary, of which irrigation with sodium hypochlorite solution is probably among the best at present available.

Hospital Infection of Wounds

Mention has been made on p. 33 of the problem of " hospital cross-infection " of wounds. Some aspects of this danger and its control have already been discussed, and others will be dealt with elsewhere in this Report (pp. 266-272).

In extension of studies of " hospital cross-infection " organised by the Council before the war, and reviewed in the Annual Report for 1938-39, the War Wounds Committee and the Committee of London Sector Pathologists initiated, in 1940, an intensive series of combined clinical and bacteriological investigations of the incidence and mode of spread of streptococcal and other infections in wounds treated in hospital; these included observations of the bacterial flora of air-raid injuries at various periods after their infliction. It is not possible to list here the names of all the surgeons and pathologists who took part in these important studies, but an indication of the scope of the inquiries (with the names of some of the collaborators) is given in the list of publications on p. 341.

The reports on cross-infection by Professor A. A. Miles, Dr. E. T. C. Spooner, Dr. Joyce Wright, and their colleagues, made early in the war, which dealt with investigations in which the newer methods of typing *Streptococcus pyogenes* and *Staphylococcus aureus* were employed, clearly demonstrated a high degree of cross-infection of wounds, which hitherto could only be inferred from more equivocal evidence; in many cases the immediate and remote sources of infection could be traced in detail, and the risks of cross-infection from them guarded against with some precision.

The general conclusion reached from these co-ordinated studies was that a large proportion of streptococcal and other infections was avoidable if rigid

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hygienic precautions were taken during the first few weeks of treatment of the wounded or burned patient, but that the prevention of such infections demanded a very strict discipline in the performance of dressings. This conclusion led to the publication—under the joint authority of the War Wounds Committee and the Committee of London Sector Pathologists—of the pamphlet " The Prevention of ' Hospital Infection ' of Wounds " (*M.R.C. War Memorandum* No. 6), and to the drafting of a set of " rules for aseptic dressing technique " which was widely distributed by the Service and civilian health departments to hospitals in Britain and overseas. The work on the prevention of hospital cross-infection has since been extensively developed in various directions, particularly in regard to such questions as air purification in Units for the treatment of burns and other types of open injury. The investigations of Dr. R. B. Bourdillon and Dr. Leonard Colebrook, of the Council's staff (pp. 215 and 271), are of particular interest in this connection.

Studies of the incidence and prevention of both direct and cross-infection in wounds sustained in civil life—especially industrial injuries—are described in the report of the special Wound Infection Unit (p. 266), established by the Council at the Birmingham Accident Hospital and Rehabilitation Centre in 1942. Work during the war on the control of " hospital cross-infection " in its wider aspects is discussed on pp. 195-196.

Emergency Amputations

In the summer of 1940 there was considerable argument among surgeons on the subject of " guillotine " amputations, some contending that they should not be done in any circumstances, others maintaining that when performed for the proper indications, and followed by adequate skin-traction, they had certain limited but noteworthy advantages. With the aim of clarifying the issue, the War Wounds Committee appointed a sub-committee of general and orthopaedic surgeons to consider the whole question of limb amputations for war surgery. The agreed recommendations, endorsed by the main Committee and approved by the Inter-Services Medical Editorial Committee, were published in 1941 under the title of " Emergency Amputations " (*M.R.C. War Memorandum* No. 5).

Experience showed that, as the war progressed, guillotine or other circular amputations were less and less frequently resorted to, since it was generally possible to make skin-flaps, and severe infections of the types which may demand urgent primary amputation, with the intention of re-amputation later, became progressively rarer with the successful use of chemotherapy.

Experimental Work on Wounds: Co-operation of Clinicians and Laboratory Workers

From the beginning of the war, there was a natural tendency for laboratory research workers, normally engaged in whole-time investigation in one or other of the biological sciences, to direct their attention to practical problems of war surgery, more particularly to the physiology of wound healing. As might be expected, the Council received numerous requests from biologists wishing to be put into touch with clinicians with whom they might usefully co-operate, and it was agreed that one of the earliest functions of the War Wounds Committee should be to make a comprehensive survey of relevant laboratory investigations in progress in Great Britain, and to arrange a Conference at which the research workers concerned could meet surgeons and pathologists, so as to exchange views. The survey was undertaken for the Committee by Professor Florey and Professor J. Paterson Ross, and, on the basis of their report, invitations were issued to a very large number of laboratory workers and clinicians to meet in Conference at the London School

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of Hygiene and Tropical Medicine on the 29th November, 1940. A detailed abstract of the proceedings of this Conference was published in the *Bulletin of War Medicine*, 1941, **1**, 129-136.

It has become clear that much valuable collaboration between laboratory workers and clinicians resulted from the Conference, and that laboratory methods originally devised for other purposes were in several instances successfully adapted to researches on practical problems of wound treatment. Among the more interesting of the investigations directly arising from the Conference, or influenced by it, have been Dr. P. B. Medawar's studies of the uses and limitations of skin homografts (p. 345), and the work in which he collaborated with Dr. F. Jacoby, of Birmingham, and Mr. E. N. Willmer, of Cambridge, upon the effects of sulphonamides and aminoacridines upon cells grown in tissue culture. Studies of several newer antiseptic and chemotherapeutic substances, on similar lines, have since been made by Dr. Jacoby. Other experimental work bearing on practical problems of war surgery was done by Dr. Honor B. Fell (p. 371) and her colleagues at Cambridge (the physiology of wound healing, and the influence of various agents upon it; the mechanism and prevention of keloid scarring). Workers who contributed to the discussions at the Conference have also studied such problems as the resistance of granulation tissue to the absorption of toxins (Professor D. F. Cappell, p. 344), and the possible influence of nutritional deficiences on wound healing.

Healing of War Fractures

A special sub-committee of the War Wounds Committee was established in 1942, to consider whether the healing-time of long-bone fractures sustained during the war was as satisfactory as could be expected on the basis of earlier experience; to review existing knowledge and to issue instructions regarding the causes and prevention of delayed bone-healing; and to direct or co-ordinate new researches on fracture treatment. Mr. H. A. T. (now Sir Thomas) Fairbank was appointed Chairman of this body. Early in its work, the sub-committee prepared two memoranda, upon "The causes and prevention of delayed union of fractures", and "The avoidance of infection around transfixation pins", respectively, which were published as special articles in the *Bulletin of War Medicine* (1944, **4**, 559-61). A circular on the points to be noted in the clinical records of fracture cases was also drafted, and this was issued by the Ministry of Health to E.M.S. fracture and orthopaedic centres in England and Wales.

In August, 1943, the sub-committee received, through the Medical Research Council, a request from the War Office that it should arrange and supervise the clinical application of the researches being carried out by Captain G. Blum (later Major Blaine), R.A.M.C., with an expenses grant from the Council, on the rôle of phosphatase in the healing of fractures, and on the use of plastics in bone work. Captain Blum was working at this time in Professor Samson Wright's department at the Middlesex Hospital, where he had the co-operation of Dr. D. Slome. By injecting phosphatase and glycerophosphate in an alginate "anchoring medium" at the site of a fracture, he had demonstrated experimentally that callus formation could be accelerated, but the clinical application of this study still awaits the availability of a phosphatase preparation in sufficient concentration.

Of the many different non-absorbable plastics tested by Captain Blum and his colleagues as possible alternatives to metals for bone-plating, the most promising from the surgical point of view seemed to be methyl methacrylate. Although this had no obvious advantages over metals for the usual plating procedures and was definitely weaker, experiments at the Middlesex Hospital

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showed that it could be inserted into the tissues in the form of a " dough " then hardened *in situ* by irradiation with ultra-violet rays; this finding suggests that the plastic might, in carefully selected cases, be used as a permanent internal splint for the human spine. Reports on various aspects of the work carried out with absorbable and non-absorbable plastic materials during the war years have been published by Blaine (pp. 344-5) and others.

Following a request from the British Orthopaedic Association in 1943, that the Council should sponsor research on improved methods of bone-plating, and assist in standardising the appliances and procedures used for this purpose, a series of conferences was held between surgeons, biologists, chemists, metallurgists, engineers and a representative of the surgical instrument manufacturers (Mr. H. G. Drew), who submitted detailed specifications of bone plates, screws and other relevant appliances, for discussion. Dr. D. P. Cuthbertson (p. 12) acted as Secretary of these conferences, and as co-ordinator of the work arranged at different centres. The primary object of the studies was to find a more readily available, and more easily workable, metal than vitallium for bone-plating; but the possibility of using plastics in bone repair was also further considered with various experts.

Tissue culture experiments with a number of promising metals (osteoblasts from chicks' frontal bones being used) were carried out by Dr. Honor B. Fell at the Strangeways Research Laboratory, Cambridge, and three metals (or metal alloys) were selected as being apparently the most inert, and suitable for further tests in animals. Shavings of 12 different alloys, in addition to vitallium, were placed in human serum and incubated at 37°C. for varying periods up to three months by Miss M. E. Mackay at the Lister Institute, London. The samples of serum were then subjected to spectrographic tests for various metals, in the Metallurgy Division of the National Physical Laboratory, by arrangement with the Department of Scientific and Industrial Research. The proposed long-term experiments *in vivo* with metals selected for further tests could not be undertaken during the war period, but it is hoped to continue this research as opportunity offers.

The problem of determining the best design of screw for bone work—i.e. the screw with the largest area of contact between metal and bone—has received much attention. It was thought that as the absorption of bone under pressure, and the melting of ice under pressure, were not entirely dissimilar, tests of the holding power of various types of screw frozen into ice might be informative. The necessary apparatus was designed in the Engineering Division of the National Physical Laboratory, and the experiments were undertaken as a preliminary to appropriate tests of selected screws inserted into living bones. The question of the best type of screwhead for bone-plating has also been studied.

Injuries to Blood Vessels

In the spring of 1944, the Council were approached by the War Office with a request that they should appoint a special sub-committee to direct research on vascular injuries (i.e. injuries to major blood vessels) at the principal centres for the treatment of these which were being set up in Britain as part of the Emergency Medical Services scheme in preparation for " D-day." This sub-committee (p. 414), of which the late Sir Thomas Lewis, F.R.S., was the first Chairman, was responsible for producing the memorandum " Arterial Injuries: Early Diagnosis and Treatment " (*M.R.C. War Memorandum* No. 13). An account of the treatment of traumatic false aneurysm and arteriovenous fistula, prepared by Mr. B. C. Maybury on behalf of the sub-committee, was published as a special article in the *Bulletin of War Medicine* (1945, **5**, 417-422).

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Various researches on the effects and treatment of injuries to blood vessels were carried out by clinical members of the sub-committee at the centres under their direction, and arrangements have been made for the follow-up, over a long period of years, of patients who have suffered such injuries, particularly those in whom arterial ligation has successfully been performed.

After a visit by Professor J. R. Learmonth and Captain P. L. Mollison, R.A.M.C., to 21 Army Group in 1944, provisional arrangements were made with the War Office for Captain Mollison to make clinical and physiological observations upon cases of vascular injury and of traumatic anuria in the field. These arrangements fell through, owing to the speed of the Allied advance into Germany, and the lack of suitable cases, but Captain Mollison was able, instead, to obtain some interesting data on blood changes in the victims of Belsen Concentration Camp (p. 129), and to take part in their treatment.

Pathological Specimens of War Injuries

In 1941 the Council accepted a request from the War Office and the Royal College of Surgeons of England that they should assist with arrangements for forming a comprehensive National Collection of Pathological Specimens illustrating the injuries and diseases of war. The need for a co-ordinated effort to this end had been appreciated from the beginning of hostilities, but it was regrettably emphasised in May, 1941, when almost the whole of the Army Medical War Collection, made between 1914 and 1918, and housed at the Royal College of Surgeons, London, was destroyed by enemy action; it is of interest to recall that the Council's predecessors (the Medical Research Committee) had played a large part in the organisation of this collection. Following its destruction, it became necessary not only to collect specimens demonstrating the characteristic injuries and diseases of the second world war, but also, so far as possible, to replace, for purposes of record and teaching, the more important of those amassed earlier. A special sub-committee of the War Wounds Committee, under the chairmanship of Surgeon Rear-Admiral Gordon-Taylor (now Sir Gordon Gordon-Taylor), was appointed to consider means of making the scheme effective.

It soon became evident that, in order to maintain the active interest and co-operation of clinicians and pathologists in regard to the collection and proper preservation of suitable specimens, it would be necessary to appoint a whole-time temporary curator for the Collection, who would travel about Britain and, if necessary, to theatres of war overseas, from this point of view. Accordingly, on the 1st January, 1943, Miss Joan M. Ross, M.D., was appointed to this post, and the Council are glad to be able to record that her energetic efforts on behalf of the Collection were remarkably successful.

By arrangement with the War Office, Dr. Ross paid visits to the Italian front in 1944 and to the region of Belsen Concentration Camp in 1945; in the former of these visits, she was accompanied by Mr. P. G. Hennell, the colour photographer (see below), and from both she brought back many specimens of value to the Collection. A very large number of pathological specimens (over 1,500), together with photographs, drawings and other objects bearing upon the medical history of the war years, has been accumulated. The specimens are being carefully examined, classified and mounted; and, when this work is completed, it is proposed to distribute the Collection to appropriate museums or other institutions in Britain and in the Empire overseas.

Colour Photography

Before the War Wounds Committee was appointed, the Council had received a generous offer from the Metal Box Company, Ltd., to place the services of Mr. P. G. Hennell and the technical facilities of the firm's photographic

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department at the Council's disposal for the duration of the war. As the result of this arrangement, Mr. Hennell and his assistants, working for the War Wounds Committee almost on a whole-time basis during the war years, have produced an unique series of coloured photographs of wounds and injuries of different types and at different stages of treatment; they have been able to give specially useful co-operation to the surgeons at the Maxillo-Facial Centres in Britain, who have had the task of repairing the effects of burns and other mutilating injuries; they have also taken a number of photographs illustrating typical diseases of the war. By arrangement with the War Office, Mr. Hennell paid a visit to the Italian front in the spring of 1944, from which he brought back numerous photographs, illustrating, among other things, the clinical applications of penicillin in the treatment of war wounds of different kinds. A selection of the photographs and drawings of injuries and diseases accumulated from various sources during the war period has been made by a special sub-committee, for purposes of permanent record and display. It has been arranged between the Council and the Royal Society of Medicine that the Society will house the " master set " of selected pictures, and make it available for reference by interested workers.

Scottish and Northern Ireland War Wounds Committees

A Scottish War Wounds Committee and a Northern Ireland War Wounds Committee were appointed in 1941 and 1942, respectively, to advise on studies of war wounds, particularly in air-raid casualties, in Scotland and Northern Ireland. Professor J. R. Learmonth was Chairman of the Scottish War Wounds Committee, and Professor P. T. Crymble Chairman of the Northern Ireland War Wounds Committee. Both these bodies had the formal status of sub-committees of the Council's War Wounds Committee, and they reported to the latter on matters of common interest.

Other Activities of the War Wounds Committee

It is not possible to deal in detail here with all the practical questions which were considered at the fifteen meetings of the main War Wounds Committee, and at the many more meetings of its sub-committees and informal conferences, but some of the more important of these may be mentioned.

Soon after it was appointed, the Committee arranged a series of clinical trials of a British-made equivalent of the German drug " Dolantin " or " Dolantol " as a synthetic substitute for morphine in the relief of pain or of muscular spasm. Investigations of the drug were organised with the co-operation of the Ministry of Health and of the Service Departments, and a report on the trials at a number of E.M.S. hospitals was published by Professor R. V. Christie (*Lancet*, 1943, **i**, 294). The drug was also tested in neurological cases, by Dr. G. Fitzgerald and Dr. B. McArdle in the Neurological Research Unit at the National Hospital, Queen Square, London (p. 263). The results of the various studies showed that the drug had definite value as an analgesic and antispasmodic, and it has since been placed upon the British market under the non-proprietary name of pethidine.

In December, 1940, the War Wounds Committee joined with the Committee on Traumatic Shock (p. 415) in appointing a sub-committee to investigate the incidence and causation of renal failure (traumatic anuria) following crushing injuries as typically seen in air-raid casualties. Attention had been drawn to this problem by the observations of Dr. E. G. L. Bywaters and his colleagues at the British Postgraduate Medical School, London, which are discussed in greater detail on p. 51. As an outcome of the sub-committee's investigations, and of the clinical and experimental work of Dr. Bywaters and others, provisional instructions for the first-aid and later treatment of these cases

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were issued by the Service and civilian health departments to medical officers in the Fighting Services and the Emergency Medical Services, respectively, and to A.R.P. personnel through the Ministry of Home Security. Research on the causative factors in traumatic anuria has since been continued by various workers.

The War Wounds Committee had under consideration from time to time a number of reports claiming favourable results from use of Doljanski's "heart extract powder" (H.E.P.) as a means of accelerating the healing of indolent wounds. In an attempt to confirm these claims, experimental work with H.E.P. and similar substances was kindly undertaken for the Committee by Professor J. S. Young (p. 344), Dr. A. H. Cruickshank, Professor J. N. Davidson and others. A report by Professor Young, Dr. Cruickshank and Dr. W. J. Martin, which has been published (p. 330), records the interesting conclusion that H.E.P., so far from accelerating the healing of healthy experimental wounds, definitely retarded their healing; its effect, when applied to the surface of a wound, was to produce a non-specific foreign-body reaction, similar to that evoked by the two azo dyes, Scharlach R and Sudan III, "which enjoyed a vogue some 30 years ago as stimulants to the healing of indolent wounds." Any effect which H.E.P. may have upon indolent wounds seems likely therefore to be non-specific, and due simply to the fact that it is a foreign material.

Another matter considered by the War Wounds Committee was the "terminology of wound closure"—i.e. the proper use of the terms "primary," "delayed primary" and "secondary" suture (or closure) of wounds. The views of members of the Committee on this controversial subject were incorporated in a statement prepared for the Army Medical Department, which was published in the *Bulletin of War Medicine*, 1945, **6**, 62.

The Committee co-operated with other committees of the Council in arranging clinical tests of the haemostatic and other properties of Cohn's fibrin foam and human thrombin, and of similar products since produced in Britain, including the use of fibrinogen for nerve-suture. In consultation with the Anaesthetics Sub-Committee of the Traumatic Shock Committee, the War Wounds Committee also made arrangements with the Service Departments for field trials of the uses and limitations of regional procaine analgesia for the treatment of war casualties.

The Committee and its sub-committees gave much practical advice to Service and other Departments on such diverse questions as the dosage of gas gangrene antitoxins, and measures of war-time economy in the uses of surgical rubber gloves and surgical spirit; and they dealt with a large number of applications by manufacturers for clinical trials of particular products or appliances.

A special Sub-Committee on Chest Injuries, under the chairmanship of the late Mr. A. Tudor Edwards, gave useful advice to the Medical Department of the British Council on the production of a film dealing with thoracic surgery.

The Treatment of Burns

Heat burns and scalds—A very wide programme of research on the pathology and treatment of burns was sponsored by the Council during the war. Initially, an informal "co-ordinating team", to assess the results of current methods of treatment, was set up under the aegis of the War Wounds Committee in 1940. The main reason for the appointment of this team was the evidence which quickly became available under war conditions that the use of tannic acid, as generally recommended at the outbreak of hostilities, was unsuited to the treatment of the typical aviator's burns, involving the face and hands; it prevented that early movement of the

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eyelids and fingers which is considered so important in the care of these injuries, and, if associated with infection beneath the eschar, was liable to lead to scarring, deformity, or even, through interference with the blood supply, to gangrene of the finger tips. Later, as will be shown below, the tannic acid treatment of deep or extensive burns was found to have other dangers, and the use of tannic acid for the treatment of burns in any site was all but abandoned in British Service and civilian practice.

The anomalous position was thus reached early in the war, that it was necessary to discard the method of local treatment which had been most favoured in peace-time, and to attempt to devise satisfactory alternatives. To this end, the " co-ordinating team " initiated studies of the uses and limitations of treatment by means of sulphonamides locally and saline baths; and a small Unit was established by the Council at the Radcliffe Infirmary, Oxford, in 1941, to investigate the possibilities of certain other methods. The studies made in this Unit between June, 1941, and September, 1942, by Dr. J. M. Barnes and his colleagues, included clinical trials of the " closed plaster " treatment (p. 33), combined with postural drainage, for burns of the limbs. Although good results were obtained with this method under the careful conditions of its application at Oxford, it was considered by many surgeons to involve too many hazards for general use in war burns; in particular, like the tannic acid treatment, it prevented early movement of the joints and tendons. In the special centres set up by the Royal Air Force and the civilian Emergency Medical Services for the treatment of burns in aviators and others, chief reliance (until the advent of penicillin treatment) was, therefore, placed instead upon the local use of sulphonamides, together with saline baths; the danger of a toxic degree of absorption of sulphonamides from the damaged area into the blood-stream, shown subsequently to occur with extensive burns, did not apply to the same degree in the case of burns of limited extent, such as those of the hands. With regard to Dr. Barnes's clinical studies of the closed plaster treatment, it is of interest to note that experiments made afterwards by Professor G. R. Cameron and his colleagues (see below), following the line given by Drinker and others in America, showed that pressure applied with plaster bandages to experimental limb burns in goats was of value both in saving life and in accelerating healing; it may be, therefore, that there is still a place for " closed plaster " in the treatment of burns in sites where early movement is not a consideration; it is, at least, one means of applying the " pressure " to burned areas which is nowadays considered so important in the restriction of plasma loss after burns, and it can be combined with the systemic use of penicillin or other chemotherapeutic agents.

Among other studies made by Dr. Barnes in the Unit at Oxford were tests of various synthetic detergents for cleansing and disinfecting burns and the surrounding skin; the substances examined included cetyltrimethylammonium bromide (later known as " Cetavlon "); following Dr. Barnes's favourable report, and confirmatory work at other centres, " Cetavlon " has been widely used for this and many other purposes in surgical practice.

It soon became apparent that the problems of the pathology and treatment of burns and their systemic effects were so manifold and complicated that an intensive scheme of co-ordinated laboratory and clinical research was called for. A special Burns Sub-Committee of the War Wounds Committee (p. 414) was accordingly appointed in 1942, to organise investigations on these lines. It included representatives of each of the Fighting Services, the Ministry of Health, the Department of Health for Scotland, the Ministry of Home Security, and the Ministry of Supply, as well as the Council's own nominees. Among those serving upon it were the surgeons in charge of several of the centres

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for the treatment of burns and maxillo-facial injuries in Britain; this provided useful co-operation and co-ordination in the clinical trial of new methods of treatment. Prominent among the researches carried out for the Sub-Committee were the important series of experimental investigations in Professor R. A. Peters's department at Oxford, on the problem of " burns toxaemia " and on the metabolic effects of burning; the investigations undertaken by Professor Cameron and his colleagues at the Chemical Defence Research Experimental Station, Porton, by kind permission of the Ministry of Supply, on phosphorus burns, on the toxicity of various local applications used for thermal injuries and on the treatment of burns by " pressure " methods; and the extensive scheme of clinical and bacteriological studies of burns and scalds, directed by Dr. Leonard Colebrook, of the Council's staff, in the Burns Unit, Royal Infirmary, Glasgow, from 1942-43 and subsequently in the Burns Unit at the Birmingham Accident Hospital and Rehabilitation Centre. Some of the studies are noticed in greater detail below. In addition—in a field where the interests of the Burns Sub-Committee overlapped those of the Military and Royal Naval Personnel Research Committees—special mention should be made of the hazardous work on methods of protection against flame-throwers carried out by Dr. R. B. Bourdillon of the Council's staff (pp. 136 and 209).

Soon after the Burns Sub-Committee was appointed, Professor (then Lieut.-Colonel) W. C. Wilson (a member of the Sub-Committee) submitted a memorandum to the Council and the War Office, calling attention to the potential danger of liver damage if tannic acid was applied to deep and extensive burns. His experimental studies in the production of hepatic necrosis by the injection of tannic acid and tannates into animals were confirmed and extended by Dr. Barnes, Dr. R. J. Rossiter and Mr. E. J. Clark, at Oxford, and by Professor Cameron and his colleagues. Independent observations made in Canada and the United States led to similar conclusions regarding the risks of tannic acid treatment for severe burns, and, as indicated above, this method of treatment was thereafter largely discarded. It is probably safe for use only in small or superficial burns, treated under good conditions, and the need for it has been obviated by the discovery of better methods of local treatment, as the result of the extensive programme of research on this subject carried out in Britain, the Dominions and the United States during the war years.

There has long been argument as to whether there is a true " toxaemia " of burns, independent of the now recognised toxic effects of tannic acid treatment, and of the toxaemia which may be associated with severe bacterial infection. Research on this problem by Professor Peters and his colleagues started from the hypothesis that enzymes or other substances liberated from the tissues damaged but not coagulated by heat, towards the margins of a burn, might themselves act as systemic poisons. At the outset of these studies, the workers at Oxford developed a method for producing standard experimental burns at known temperatures, which was used in interesting observations of the microscopic changes in and around skin burns, and in many other studies of the local and systemic effects of severe burning. It is not possible to discuss all these investigations here, but they have been reviewed by Professor Peters in an article in the *British Medical Bulletin* (1945, **3**, 81). The finding that a proteinase is among the substances liberated from the skin after burns may well have a bearing on the problem of blister-formation in these injuries, and it is of interest in relation to the still unproven hypothesis of burns " toxaemia " mentioned above, though the fact that the blood normally contains an active " anti-proteinase " makes it unlikely that the proteinase is itself capable of producing damage to the internal organs. Of greater immediate importance in regard to the treatment of war burns were the studies by Professor Peters and his colleagues of the metabolic effects of severe

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burning (see list of publications on p. 347). The work of Rossiter and Peters on the control of oedema formation after burns in small animals, by the application of moderate external pressure, was also of great interest, in relation to Professor Cameron's subsequent work in goats, and to the increasingly wide adoption, in the U.S.A., the Dominions and this country, of treatment by " pressure dressings " for human burns.

An account of the establishment by the Council of special Units for clinical and laboratory research on burns in man, first (from 1942-43) at the Royal Infirmary, Glasgow, and later at the Birmingham Accident Hospital and Rehabilitation Centre, is given on p. 270. The studies made in those Units by Dr. Leonard Colebrook and his colleagues have related mainly to the prevention and treatment of infection in burns and scalds, and to the control of burns " shock " by fluid replacement. An important investigation undertaken in the Glasgow Unit, for the Burns Sub-Committee, had as its object the devising of a simple and efficient " first-aid " treatment for burns. There is general agreement that all patients with severe or extensive burns should, when possible, be sent to well equipped hospitals without delay, and without preliminary " first-aid " treatment of their injuries. There are, however, circumstances, particularly in warfare, in which it is impossible for the burned patient to be taken immediately to hospital. For use in such cases, and in patients with minor burns involving no risk to life, the workers at Glasgow devised a cream of which the active ingredients were sulphanilamide and cetyltrimethylammonium bromide. Following extensive clinical tests, of which the results were published in the Council's *Special Report Series* No. 249 and in various papers in scientific journals, this preparation—known as the " Glasgow No. 9 Cream "—was widely adopted for the treatment of Service and civilian casualties. For the local treatment of burns in hospital, Dr. Colebrook and his colleagues used initially a sulphonamide cream, and latterly one containing penicillin as well. This treatment is applied with rigid aseptic precautions, after the control of " shock " by transfusion; it is combined with the use of pressure dressings, changed infrequently, and is followed by early skin-grafting. In recent studies of air hygiene in relation to the dressing of burns, Dr. R. B. Bourdillon, of the Council's staff, has collaborated with Dr. Colebrook and his colleagues at Birmingham (p. 215).

The experiments made for the Burns Sub-Committee by Professor Cameron and other workers at Porton on the toxicity of tannic acid, and on the treatment of limb burns by " pressure " applied as plaster bandages, have already been mentioned. In addition, Professor Cameron and his colleagues published useful studies of the toxicity of gentian violet and of propamidine preparations as used for the treatment of burns. They also had a major share in the investigations of the effects and treatment of phosphorus burns, described below.

A review article prepared for the Burns Sub-Committee by Dr. R. J. Rossiter, on the problem of plasma loss in burns, was published in the *Bulletin of War Medicine* (1943, **4**, 181-189), and one by the Secretary of the Burns Sub-Committee (Dr. F. H. K. Green), on the main trends in the local treatment of thermal burns (during the war), was published in the *British Medical Bulletin* (1945, **3**, 91-95) and the *Bulletin of War Medicine* (1945, **5**, 605-613).

Chemical burns.—Studies of chemical burns, such as those due to war gases, have been mainly the concern of the Ministry of Supply, but close co-operation has been maintained between the Ministry and the Council in this field, and the Council have supported certain work on mustard gas injuries (p. 387). Moreover, as already mentioned, representatives of the Ministry served upon the Council's Burns Sub-Committee. The brilliant researches by Peters, Stocken, Thompson and colleagues at Oxford which led

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to the discovery of 2:3-dimercaptopropanol—subsequently named "BAL" (British Anti-lewisite) in America—as an effective antidote to lewisite and other forms of arsenical poisoning, and to poisoning by various metals, were originally undertaken for the Ministry, but subsequent investigations into the therapeutic applications of BAL and related substances, outside the sphere of war gas injuries, were sponsored by the Council by arrangement with that department. A preliminary report on 30 cases of arsenical dermatitis treated with BAL was prepared for the Council at the request of the Army in 1944 (*J. clin Invest.*, 1946, **25**, 497), and the Council have since organised further clinical trials of this treatment in cases of arsenical poisoning.*

In regard to research on phosphorus burns—a type of injury involving both chemical and heat effects—the liaison between the Council's Burns Sub-Committee and workers for the Ministry of Supply at Porton was particularly close. Recommendations on the first-aid treatment of phosphorus burns, based on work done for the Sub-Committee by Professor Cameron and his colleagues at Porton and by Dr. Bourdillon at the National Institute for Medical Research, were adopted by the medical departments of the Fighting Services, and by the Ministry of Health and Ministry of Home Security in respect of the treatment of these burns in civilian air-raid casualties.

Studies in the Department for Research in Industrial Medicine at the London Hospital, of burns due to methyl bromide as used in certain fire-extinguishers, are mentioned on p. 315.

Research Committee on Air-raid Casualties: "Blast" Injuries: Wound Ballistics

A research Committee on Air-raid Casualties (p. 414), appointed jointly by the Council, the Ministry of Health and the Ministry of Home Security, assisted the two latter departments in analysing the nature of the injuries produced by bomb "incidents" of different types. In particular, it sponsored work on the pathology and effects of "blast injuries," by arranging for expert examination of the small amount of post-mortem material from human sources that was available. Research on blast effects, and wound ballistics, carried out for the Military Personnel Research Committee and its Sub-Committee on Weapons (Biological Assay) is noticed on p. 138. Much of the experimental work done in Great Britain during the war on these subjects was carried out by Professor S. Zuckerman and his colleagues at Oxford and elsewhere, on behalf of the Research and Experiments Branch of the Ministry of Home Security, and with support from that department. Studies of under-water blast injuries were undertaken by the Admiralty and the Ministry of Supply, the Royal Naval Personnel Research Committee (p. 147) being kept informed of their progress.

The Work of the Brain Injuries Committee

A Committee, under the chairmanship of Professor E. D. Adrian, was appointed early in 1940 to advise and assist the Council in the promotion and co-ordination of research on wounds involving injuries to the brain. The three Fighting Services, the Emergency Medical Services and the Ministry of Pensions were represented upon it; a list of the members is given on p. 415.

One of the first matters to which the Committee directed attention was the need for keeping accurate and detailed case-histories of patients with brain injuries, and the arrangements made for this purpose at the special centres which had been established for the treatment of head injuries in Service and civilian patients were carefully scrutinised and correlated. The preparation of a series of critical reviews on different aspects of head injury, based on published

* For a recent official statement on BAL see *Lancet*, 1947, **ii**, 497; *Brit. med. J.*, 1947, **ii**, 520.

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data, was undertaken by members of the Committee and their colleagues, as a preliminary to drawing up plans for further research in this field.

To facilitate the work of the main Committee, several sub-committees were formed to deal with different aspects of brain injuries and their effects. Among the problems examined in this way were (*a*) the assessment of the psychological state of patients after head injuries; (*b*) the relationship of head injury to subsequent epilepsy; (*c*) the use of electro-encephalography as an early diagnostic measure in cases of post-traumatic epilepsy; (*d*) the prevention and treatment of headache and other complications following head injury; (*e*) questions relating to the disablement and rehabilitation of patients with brain injuries. Schemes for research at the special head injury centres and elsewhere were formulated by the sub-committees, and arrangements made for the co-ordination and extension of investigations already in progress. Among these, the studies of the effects of different antiseptics on brain tissue, made by Dr. Dorothy S. Russell of the Council's staff and her colleagues, at the Head Injuries Centre at Oxford directed by Brigadier H. Cairns, deserve special mention; a summary of Dr. Russell's work on this and other problems of neuropathology is given on p. 332.

In relation to the work of the sub-committee dealing with the assessment of psychological states after head injury, a glossary of the psychological terms commonly used in recording such cases was prepared by the Committee, with the object of securing a greater measure of uniformity in terminology; it was issued by the Council in 1941 as *M.R.C. War Memorandum* No. 4. This sub-committee also undertook the task of drawing up a list of suitable psychological tests for use in the clinical examination of patients with head injuries.

The Committee arranged for clinical and experimental studies of brain injuries, their effects and treatment, to be carried out at a number of centres, and for an inquiry to be made into the effects of travel on patients in the acute stage of such injuries; it was concluded that these patients, unless very deeply unconscious, stand travel well, both before and after operation, and that their transport from the scene of injury to special centres where they can receive expert neurosurgical attention is therefore advisable. A memorandum on head injuries in air-raid casualties, drawing special attention to the potential dangers of scalp wounds, was prepared for the Committee by Professor G. Jefferson, and circulated to the Service and other interested Government Departments, for the guidance of medical officers; its conclusions were emphasised in a subsequent paper by Lieut.-Colonel E. H. Botterell, R.C.A.M.C., and Professor Jefferson, which was published in the *British Medical Journal*, 1942, i, 781.

In parallel with the tests of the value of sulphonamides for the prevention and treatment of wound infections, carried out for the War Wounds Committee (p. 34), the use of these drugs in head wounds was investigated at the National Hospital, Queen Square, London (p. 262), at Oxford and elsewhere. A warning was issued on the danger of applying sulphathiazole to the brain, owing to its tendency to produce convulsions. Members of the Brain Injuries Committee took a leading part in testing the clinical value of penicillin in the treatment of head wounds, and they co-operated in the clinical trials in this country of fibrin foam, human thrombin and related products as agents to control bleeding (p. 194).

Liaison was established with the Military Personnel Research Committee (p. 134) on the question of protection against head injury, and with the Air-Raid Casualties Committee (p. 47) on the subject of blast in relation to injuries of the nervous system.

Particulars of the research grants made by the Council, on the recommendation of the Committee, for specific investigations on head injuries are given on pp. 347-349.

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The Work of the Nerve Injuries Committee

The Nerve Injuries Committee—originally set up in October, 1940, as the Peripheral Nerve Injuries Sub-Committee of the Brain Injuries Committee (see above)—was appointed, under the Chairmanship of Brigadier G. Riddoch, to advise and assist the Council in the promotion of research on war injuries involving the peripheral nerves; the Committee's terms of reference were later broadened to include also problems relating to spinal injuries. The membership of the Committee is given on p. 415.

An important feature of the Committee's work was that it was carried out from the outset in close liaison with the activities of the special centres established by the Emergency Medical Services for the treatment of peripheral nerve injuries. It was thus possible to make plans at an early stage for a comprehensive follow-up scheme, with the co-operation of the three Fighting Services, the Ministry of Health, the Department of Health for Scotland, the Ministry of Pensions and the Ministry of Labour and National Service. Under this scheme, arrangements were made for research on specific problems at the special centres, and for patients to be re-examined at frequent intervals after discharge from hospital. In formulating the follow-up scheme, the Committee drew attention to the need for a complementary scheme for the after-care and rehabilitation of patients with injuries to the peripheral nerves, and their recommendations on this aspect of the problem of nerve injuries were transmitted to the Government Departments concerned.

With the object of securing uniformity in recording case histories, in methods of testing for peripheral nerve lesions, and in the assessment of their recovery, the Committee prepared memoranda on these subjects for the guidance of medical officers. Arrangements were also made with the Emergency Medical Services for the printing and distribution of standard outline sensory charts for use in case-records, as well as of charts for summarising the degree of voluntary power and the electrical reactions of affected muscles.

As a result of the measures outlined above, a mass of reliable data on peripheral nerve injuries has been compiled at the special centres, and the follow-up scheme is still in progress. A start has been made on the analysis of the collected case-records, with a view to the ultimate preparation of a full report on the results of the follow-up.

Following the appointment of an *ad hoc* sub-committee on spinal injuries, a series of reviews on different aspects of the subject was undertaken for the Committee by Mr. R. Barnes and Mr. A. S. Kerr, Dr. L. Guttman, Dr. S. P. Meadows and Mr. E. W. Riches. Mr. Riches's review dealing with the treatment of the paralysed bladder resulting from spinal injury was subsequently published in the *British Journal of Surgery* (1943, **31**, 135). The controversial question of the care of the paralysed bladder was given further consideration by the Committee, whose recommendations on the subject were incorporated in a memorandum on first-aid and early treatment in traumatic paraplegia. This memorandum was brought to the notice of medical officers in the Fighting Services and the Emergency Medical Services, and was published in the *Bulletin of War Medicine* (1944, **4**, 431).

With a view to the eventual use of case-records for research purposes, the Committee drew up a scheme for note-taking in spinal injuries with neurological complications, details of which, together with a skeleton form for summarising the recorded notes, were circulated to Service and civilian medical officers in charge of patients with spinal injury, by permission of the respective Medical Directors-General.

An investigation was made, with the co-operation of surgeons at a number of centres throughout the country, into the value of operative treatment for

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sciatica caused by prolapsed intervertebral disc, particularly in Service patients. The investigation was based on a scheme drawn up by the Committee, and it included a follow-up system for which the administrative machinery already in use for peripheral nerve injuries was employed. Although the result was inconclusive, the inquiry has provided much useful information. The following reports by some of the surgeons taking part have already been published or submitted for publication:—G. L. Alexander—*Edinb. med J.*, 1947, **54**, 14; B. H. Burns and R. H. Young—*Lancet*, 1945, **ii**, 424; G. F. Rowbotham—*J. Neurol. Neurosurg. Psychiat.* (in the press).

Brief particulars of the research grants for studies of nerve injuries made by the Council to the following workers are given on pp. 349-351:—

Mr. M. Abercrombie, Dr. P. Bauwens, Mr. (now Professor) F. H. Bentley, Dr. L. Guttman, Dr. W. Holmes, Professor G. Jefferson, Dr. R. L. Richards, Professor H. J. Seddon, Dr. W. H. Sweet, Dr. A. G. M. Weddell and Mr. (now Professor) J. Z. Young.

On the recommendation of the Committee, Dr. J. Doupe was appointed temporarily to the Council's staff, to undertake research at the Peripheral Nerve Centre, Winwick, Warrington; his work there has been reported in a number of interesting publications, listed on p. 341.

The Committee kept in touch with work at different centres on the use and development of various forms of electrical apparatus for muscle and nerve stimulation before, during and after operation, both for diagnostic and for therapeutic purposes. Among those taking part in this inquiry for the Committee were Dr. P. Bauwens, Brigadier W. Rowley Bristow, Dr. G. L. Brown (p. 203), Dr. A. E. Ritchie, Professor H. J. Seddon, Mr. W. Grey Walter and Mr. J. Z. Young.

To assist medical officers to recognise the effects of injury of individual nerves, the Committee sponsored the publication of a copiously illustrated pamphlet, the material for which had been compiled by the staff of the Department of Surgery at Edinburgh University and the Peripheral Nerve Injury Centre, Gogarburn, and presented to the Committee by Professor J. R. Learmonth. This work was published, under the title of " Aids to the Investigation of Peripheral Nerve Injuries ", as *Medical Research Council War Memorandum*, No. 7 (1942): a second edition of the pamphlet, incorporating some minor amendments, was published in 1943.

The Committee were kept informed of cognate researches in the United States of America by the liaison officers of the U.S. Office of Scientific Research and Development who attended their meetings from time to time, and by the exchange of interim progress reports from individual workers in both countries. The Committee also welcomed the opportunity of having information about current practice in the handling of nerve and spinal cord injuries in the Medical Services of the Canadian and U.S. Armies, whose representatives were present at several meetings. They were indebted in particular to Lieut.-Colonel E. H. Botterell, R.C.A.M.C., and Major J. E. Scarff, M.C.A.U.S., for many valuable contributions to their activities and discussions.

Traumatic " Shock "

During the war of 1914-18 the Council's predecessors, the Medical Research Committee, sponsored much clinical and experimental research bearing on the problems of " shock " and haemorrhage in battle casualties, and special observers were sent to France to co-operate with British and American workers in the field. An *ad hoc* committee was appointed to co-ordinate the clinical and experimental studies, and accounts of some of the more important investigations were later published in the Council's *Special Report Series*.

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After the armistice in 1918, both the urgency of these problems, and facilities for their investigation, declined; and, apart from the progressive introduction of blood transfusion methods into routine surgical and medical practice, few significant advances in knowledge of " shock " and its treatment were made in the years of peace.

Accordingly, when war broke out again in 1939, the Council at once appointed a Committee on Traumatic Shock to survey the existing state of knowledge of the subject, and to direct a resumption of active research upon it. The composition of this Committee is given on p. 415; it included representatives of the Army Medical Service and of the civilian Emergency Medical Services. The first Chairman was Professor G. E. Gask; on his retirement early in 1940, Dr. A. N. Drury (p. 12) was appointed Chairman, and he was succeeded by Sir Ernest Rock Carling in March, 1943. The first secretaries were Professor F. R. (afterwards Sir Francis) Fraser and the late Professor B. A. McSwiney, who acted jointly, being later succeeded by Dr. D. P. Cuthbertson (p. 12). On the basis of the Committee's initial survey of the problem, and a number of preliminary reports received, it was decided to concentrate at first on two main types of research, namely, clinical and haematological studies of blood volume and the effects of blood loss, and the production of " shock " experimentally; work was also started on the effects of giving high concentrations of oxygen to " shocked " patients.

In the meantime, it was considered urgently desirable to prepare a concise summary of the existing practical information regarding wound " shock " and its treatment, for the guidance of medical officers who would have to deal with casualties in the fighting forces, and with air-raid casualties in civilians. The Committee, in co-operation with the Army Medical Service, accordingly drafted a pamphlet on the subject, which, after approval by the Inter-Services Medical Editorial Committee (p. 199), was published in the spring of 1940, as *M.R.C. War Memorandum* No. 1. Later, in the light of experience gained during the first four years of active warfare, a revised edition of the pamphlet was published (see p. 55).

In regard to the preparation of *M.R.C. War Memorandum* No. 1, and to many other activities, the work of the Committee on Traumatic Shock was closely correlated with that of the Council's committees on blood transfusion (pp. 184 and 188); descriptions of the methods of blood transfusion adopted for use in the Army and for civilian air-raid casualties were printed as appendices to the Memorandum. The " Shock " Committee also worked in close touch with the War Wounds Committee and its sub-committees, particularly the Sub-Committee on Burns (p. 44), and later with the Protein Requirements Committee (p. 127). A special sub-committee of the " Shock " Committee advised on problems of anaesthesia for severely injured patients, and a joint sub-committee of the " Shock " Committee and the War Wounds Committee co-ordinated the investigations of the incidence and causation of cases of renal failure following crushing injuries in air-raid casualties, which are outlined in the following paragraphs.

During the intensive air bombardment of London and other cities in 1940, a clinical and pathological condition previously unrecognised in Britain became well known in the hospitals receiving air-raid casualties; it occurred in persons who had been buried for several hours beneath masonry or other heavy débris. In a typical case, the patient, brought to hospital after being pinned down by a limb for three hours or more, showed initially some redness and blistering of the compressed limb, which later swelled. As fluid accumulated in the limb, haemoconcentration occurred and the blood pressure fell. The blood pressure level could usually be restored to normal by plasma infusions, but soon signs of damage to the kidneys appeared, and about a week after injury the patient might die in uraemia, with hypertension and with an increased

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content of potassium in the blood. These changes, it was found later, had been partly described by German authors during the war of 1914-18, but they had remained unknown in this country.

The concept of " crush injury," as this condition was at first called, arose mainly as a result of observations made by Dr. E. G. L. Bywaters and his colleagues at the British Postgraduate Medical School, London. In March, 1941, data on some 16 examples of the syndrome were published; it was noted then that necrosis of muscle was the one pathological feature, apart from the renal changes, which seemed to be common to fatal cases of this type, and that a pigment—afterwards shown to be muscle pigment (myohaemoglobin)—was present in the renal tubules and sometimes in the urine.

The incidence of the " crush injury syndrome " in air-raid casualties is thought to lie somewhere between 1 per cent. and 5 per cent. Compression by débris following bomb explosions is not, however, the only cause of the syndrome; it has been found to follow burial after mining accidents, and a similar condition was observed in victims of the shelter disaster at an " Underground " station in 1943, when the factor responsible for the compression of limbs was not débris but the weight of fallen and impacted human bodies. Moreover, a condition closely resembling the " crush injury " syndrome has been shown occasionally to follow fractures and vascular injuries sustained in battle and civilian accidents, where there is no open, contaminated wound to lead to a risk of gas gangrene. Some of the cases of renal failure following injury have undoubtedly been attributable to treatment with the less soluble sulphonamide drugs, or to mismatched blood transfusion, but apart from these and the cases definitely following " compression," there is a residuum of patients with closed limb injuries in whom ischaemic necrosis of muscle occurs and muscle pigment is demonstrable in the urine, just as in the typical cases of " crush injury." In view of this, the term " ischaemic muscle necrosis " has been suggested for the syndrome, so as to include cases where the muscle ischaemia is due to causes other than compression.

During the years 1941-43, much experimental work on this subject was done in Britain and America. Dr. J. M. Barnes (p. 44) and Dr. J. Trueta (p. 56) found that a widespread and persistent arterial spasm developed in the limbs of rabbits after the release of prolonged compression by tourniquets. Dr. E. E. Pochin, of the Council's staff (p. 249), investigated the oedema which follows obliteration of the blood supply to the skin, and Dr. Grace Eggleton, Professor F. R. Winton and others, the renal clearances following trauma and ischaemia in animals. Studies by Dr. Bywaters and his colleagues showed that, in rabbits, prolonged compression of the thigh muscles was followed by oedema of the limb, haemoconcentration and a fall in blood pressure; no muscle pigment was detected in the urine (there being no myohaemoglobin in the thigh muscles of the rabbit), and renal failure did not develop. However, if human myohaemoglobin were injected into these rabbits at the time of release of the limb from compression (or, on occasion, into uninjured rabbits in which the alkali reserve of the blood had been artificially lowered) the complete syndrome as seen in man, including renal failure, could be reproduced. Investigations in the United States have confirmed the importance of muscle pigment in association with other factors, such as " acidaemia " (and an acid urine), in the genesis of the renal failure. The demonstration of similar changes (but without pigment casts) in sulphonamide anuria and acute hydronephrosis has since given some indirect support to the view that the essential action of the muscle pigment is to damage the renal tubules, and to produce a sharp rise in intrarenal pressure, perhaps by hindering re-absorption.

Relating this hypothesis to the clinical problem of treatment, it was considered that the giving of large amounts of alkaline fluids to the patients

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as soon as possible after injury might prove successful in preventing renal failure. To this end, a mobile observation team was organised, under the general direction of Sir James Walton, with the object of reaching and treating air-raid casualties as rapidly as possible, and during 1944 and 1945, as a result of the team's work, a few cases were collected which seemed to endorse the efficacy of this regime. The number so treated, however, was not sufficient to warrant a firm conclusion as to the value of alkali therapy.

In 1941, Dr. R. T. Grant and Dr. E. B. Reeve, of the Council's staff, published some important clinical observations on a series of air-raid casualties. Their findings are summarised in the report of the Clinical Research Unit at Guy's Hospital, London (p. 252). They concluded that the term " shock," as generally applied to the acute systemic effects of injury, was so ill-defined in meaning that its use without qualification was better avoided. In their view, the only logical approach to the problem of successfully resuscitating the severely wounded lay in making a critical assessment of each case, in order to determine the total reaction of the patient to injury; they emphasised, further, that while blood loss was a very important factor in producing a state of severe illness after trauma, it was not the only one concerned.

The work of Grant and Reeve, of Bywaters, and of others who observed numerous cases of injury in 1940-41, thus threw grave doubt upon the value of attacking the " shock " problem as if wound " shock " were a single clinical and pathological entity. In consequence, several lines of investigation started for the Committee at the beginning of the war were abandoned, the workers transferring their activities to problems likely to be of greater immediate value to the war effort; among the research schemes terminated as unpromising, were the clinical studies of oxygen therapy for " shock ".

The various clinical and pathological observations on reactions to trauma had already confirmed that injuries sustained in industrial and other accidents had similar general characteristics to those incurred in air-raids or battle. Accordingly, since by 1942 the large-scale aerial attacks on London had ceased for the time being, and the accommodation for Dr. Grant's Unit at Guy's Hospital had been severely damaged earlier by enemy action, the Council made arrangements with the Royal Victoria Infirmary, Newcastle-upon-Tyne, for the Unit to be temporarily transferred there, to study the effects of industrial injuries and of road accidents. The work of the Unit during its stay at Newcastle is described on pp. 253-4.

In 1942 the War Office and the Council, on the recommendation of the Military Personnel Research Committee (p. 134), established a Medical Research Section to collect information on the health and well-being of the Middle East Forces. Professor W. C. Wilson of Aberdeen (p. 45), a member of the Traumatic Shock Committee, was temporarily seconded to the R.A.M.C., with the rank of Lieut.-Colonel, to take charge of this Section; he had working with him Drs. (Majors) A. L. Chute and E. T. C. Spooner, whose studies while members of the team are mentioned on p. 135. Among the investigations made by Lieut.-Colonel Wilson in North Africa was a detailed clinical study of traumatic " shock " in 133 men severely wounded in the battle of El Alamein. His reports to the War Office and the Council on this work were later published in summary form in the *Lancet*, 1944 **i**, 587. He concluded that the most important factor in inducing " shock " was haemorrhage, and that the early and complete replacement of the lost blood by transfusion, combined with control of bleeding, was the most successful method of treatment.

Towards the end of 1943, it became clear that sufficient clinical material for resuming extensive observations on the relative significance of blood loss, tissue damage and other results of serious injury would be found only on the battlefield. Arrangements were therefore made between the Council and the

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War Office for a special R.A.M.C. team of workers to study battle casualties in the forward area in Italy. This team, known as " British Traumatic Shock Team No. 1 " was directed by Dr. Grant, with the rank of Lieut.-Colonel. It remained in Italy from February, 1944, until June, 1945, working mainly at C.C.S. level, and studying the effects chiefly of severe limb injuries and abdominal injuries. An account of its personnel, investigations and principal findings is given on p. 254. The outstanding conclusion from the Team's work was that, both in limb injuries and abdominal injuries due to battle wounds, the circulatory disturbances resulting from blood loss were the chief cause of early death, and that early and adequate blood transfusion, continued during and after the primary operation, was the most important factor in saving life—an opinion tallying closely with those of Lieut.-Colonel Wilson and many other observers in the field. The possibility of the absorption of toxic substances from the damaged tissues playing a part in the " shock " syndrome was not discounted, but, in the view of Grant and his co-workers, its significance in the battle wounds studied was probably subsidiary to that of blood loss; nevertheless, in limb injuries, Grant found that rough measurement of the volume of tissue damaged at least provided a useful index of the amount of blood loss needing urgent treatment by transfusion.

After Dr. Grant went to Italy, Dr. Bywaters was appointed to take charge of the Unit at Newcastle, with the primary object of further investigating the rôle of tissue damage in the production of " shock " and allied states. With Dr. E. D. Barlow (p. 252) and Dr. J. K. Stead, a clinical and biochemical study of 53 cases of accidental injury was made in the Unit; the findings indicated that, in the average severe case of limb injury due to accident, tissue damage was not large compared with that seen in " crushing injury." In cases of very great severity, however, and particularly in those associated with injury to the main blood vessels to a limb, there was often a considerable amount of muscle necrosis, and some of these patients died of uraemia.

Meanwhile, a different approach to the problem of a possible " toxic " factor in " shock ", resulting from tissue damage, had been made at Sheffield. In 1942, at the Council's suggestion, a small team, consisting of Mr. F. W. Holdsworth, Professor H. N. Green (p. 351) and a whole-time assistant, was formed to investigate traumatic " shock " in the victims of industrial accidents. A detailed study of over 100 severely injured patients led to the provisional conclusion that the most important factor in treatment was early surgical extirpation of the damaged tissues. The rapid recovery following amputation of lower limbs with extensive muscle damage induced Professor Green to renew the search for metabolic factors in normal and injured muscle which might, on release into the circulation, be responsible for some part of the " shock " syndrome.

This clinical concept was supported by experimental work on ischaemic shock in rats, which also indicated that local fluid loss did not account for the whole sequence of general reactions following injury. Accordingly, many different methods were used in an effort to obtain " shock-inducing " extracts from muscle. As extractions with boiling saline most frequently gave positive results, the possibility that the " toxic factor " might undergo rapid enzymic breakdown in dying muscle was considered, and, on the basis of earlier work by Dyckerhoff and others, enzyme inactivation was attempted by rapidly immersing normal muscle in acetone. Saline extracts of acetone-ether dried muscle from several species contained a powerful vaso-depressor substance, and induced the gradual development of a " shock-like " condition when injected by routes other than the intravenous. Mrs. M. Bielschowsky and Professor Green fractionated the extracts and showed that the main active substance was adenosine triphosphate (ATP). This was one of many derivatives of nucleotide catabolism which were found, on injection into animals, to be capable of producing a state closely resembling that following

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a prolonged period of hind limb ischaemia. Those of which the biological action was examined in detail caused depression of kidney function, a pronounced fall in the basal metabolic rate and in liver glycogen, and their lethal effects could be prevented by prophylactic treatment with large amounts of normal saline. It was shown that the magnesium ion strong potentiated the shock-inducing action of such compounds and also increased the general reaction to a variety of shock-inducing measures; the onset of shock induced either by these compounds or by limb ischaemia could be accelerated by raising the environmental temperature.

Evidence of the release of such products of nucleotide catabolism from injured tissues has been obtained. Thus, the adenosine equivalent of rabbit blood was found to rise in " shock " produced by limb ischaemia, limb trauma, dehydration, burns and other forms of severe tissue damage; a rise was also noted in man following experimental limb ischaemia. A rise in the nucleotide pentose of the blood plasma has likewise been demonstrated after limb ischaemia.

With the object of determining how far these experimental findings had their parallel in cases of wound " shock " in man, the War Office and the Council arranged the formation of a " British Traumatic Shock Team No. 2 ", which, under the command of Lieut.-Colonel Green, made observations on 177 battle casualties in forward areas in N.W. Europe from March, 1945, until the end of hostilities. With the collaboration of the Army Transfusion Services, large numbers of specimens of blood and muscle were regularly flown to England for biological and chemical study in Sheffield, while many less specialised tests were done in a mobile laboratory on the spot. To sum up what proved to be a very eventful and laborious investigation, it seems certain that, in man, trauma leads to an increase in the blood plasma of substances which can be, and probably are, derived from nucleotide catabolism, a finding in agreement with the animal experiments. Incidentally, in the course of these studies, attention was directed to the problem of fat embolism, and it was later shown experimentally that both in " ATP " and ischaemic " shock " the animal becomes more susceptible to the intravenous injection of fat.

It has become increasingly obvious that, if these products of nucleotide catabolism play a part in " shock ", their action is conditioned by many other factors in severe tissue damage. Haemorrhage, local fluid loss, fat embolism, magnesium, and blood-clotting factors like thrombin and thromboplastin, for instance, all greatly increase the susceptibility of the animal to the " shock-inducing " action of ATP. It is evident that, whatever rôle nucleotide catabolites play in " shock ", their effects are part of a complex integrated mechanism requiring further study.

With the work of Wilson concluded, and that of Grant and his colleagues, of Bywaters and the Sheffield team in active progress, the main function of the " Shock " Committee became the collection and discussion of results from these and other investigations. Throughout the war period, there was a free interchange of published and unpublished information between workers in Great Britain, the Dominions and the United States, and the Committee had constantly before them the question whether any of the newer facts elicited could usefully be applied to the practical treatment of wound " shock ". In the light of fresh knowledge acquired since the war began, it was decided in 1944 that the original text of *M.R.C. War Memorandum* No. 1 required drastic revision; this was undertaken, and a new edition, produced jointly by the Council's Committees on Traumatic Shock and on Blood Transfusion Research, in co-operation with the Army Medical Service, was issued by the Council in the same year.

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A great volume of clinical, pathological and experimental evidence regarding the different manifestations and treatment of "shock" due to wounds and to burns has accumulated during the past six years, but there are still many gaps in knowledge to be filled, and the implications of many of the more important studies made by British, American and other workers during the war require correlation which is likely to be given only by further time-consuming research. Thus, the precise rôles of haemorrhage, of plasma loss, of tissue damage, of associated biochemical changes and of nervous influences, in producing the altered haemodynamics causing acute illness after injury, require to be established and integrated; and the relationship of renal failure in the "crush injury syndrome" to other forms of "traumatic" and "non-traumatic" anuria, and perhaps to the toxaemia deriving from the infective muscle necrosis of gas gangrene, has still to be fully elucidated. Nevertheless, although many of the investigations initiated during the war proved abortive, and the findings established by research remain, like the pieces of a puzzle, to be fitted together, it is certain that a much clearer appreciation of large parts of the "shock" picture as a whole has emerged, with implications of the highest significance for successful treatment. If, now that the war is over, interest in the reactions of the body to injury can be maintained, and the opportunities for research provided by the regrettably large numbers of traffic and industrial accidents can be effectively used, substantial advances may come in the near future.

In the meantime, from the practical stand-point, it can be said that during the recent war the early and adequate use of blood, plasma and serum transfusions, combined with early surgical treatment, and measures to control infection, must have saved the lives of many thousands of "shocked" patients whose prospects of recovery would have been deemed hopeless under the conditions pertaining in any previous war.

This survey of work on "shock" and kindred states would be incomplete without reference to the interesting studies published, after the end of the years under review, by Dr. J. Trueta, Dr. A. E. Barclay and others, who have an expenses grant from the Council at Oxford (*Lancet*, 1946, ii, 237). On the basis of ingenious experiments, these authors put forward the suggestion that the distribution of blood supply within the kidneys is profoundly influenced by central and peripheral nervous stimuli of different kinds, and that the diversion of blood from the renal cortex to the renal medulla resulting from such stimuli, whatever their origin, may produce sufficient cortical ischaemia to account for many forms of "traumatic" and "non-traumatic" anuria. Here again, much further research is needed to confirm the observations, and to correlate them with the results of other studies of anuria and the "shock-like" states, but their implications, if substantiated, may be far-reaching, not only in providing a common pathological mechanism for the kidney failure following many different diseases and types of injury, and perhaps in redirecting attention to the long-disputed question of the nervous factor in "shock", but also in suggesting rational new lines of treatment. Responsible experts have expressed the opinion that the chief reason why traumatic anuria was more frequently encountered in the recent war than in previous conflicts was that greatly improved methods of resuscitation enabled "shocked" patients who otherwise would have died in the first two days after injury, to survive long enough to develop it. Recent studies in Britain and elsewhere, on the mechanism of anuria and on the treatment of uraemia, may, if confirmed, provide means of saving such patients from the further and much rarer emergency of acute renal failure, and thus lead to a still higher proportion of permanent recoveries after severe injury.

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III

WAR DISEASES

In this section will be considered some of the principal diseases which constituted major problems during the war, and on which important programmes of research were supported or co-ordinated by the Council, usually with the help of expert Committees appointed specially for the purpose. It will be seen that the list of war diseases discussed here, while including some of those of greatest military significance, is by no means comprehensive; the support given by the Council to research on many other diseases is mentioned elsewhere in this Report. Thus, in the cases of many infective conditions, including venereal diseases, bacillary dysentery and some skin affections, the outstanding advances achieved during the war years consisted in the successful application of sulphonamide drugs, penicillin or both as method of treatment; the Council's substantial part in assisting the growth of knowledge under these headings, particularly in regard to the development of penicillin as a therapeutic agent, is recorded in Section IV below. In regard to numerous other conditions of great importance, investigations into causation and treatment were carried out directly by Service or civilian medical officers without need for the Council's intervention or support; field studies in the treatment of amoebic dysentery fell into this category, and so did the large number of inquiries organised by specialist medical officers in the Forces and the civilian Emergency Medical Services into the nature and treatment of the psychological effects of battle experience and air-raids; an example of a different kind was an investigation of peptic ulcer among soldiers, promoted in 1940, after discussions with the Council, by the Royal College of Physicians of London.

On some of the diseases considered in the present Section, such as malaria and tuberculosis, the Council had sponsored extensive research programmes before the war; on others, they took the initiative, under war conditions, of starting programmes of *ad hoc* research to meet a sudden emergency; on others, again, their advice and help was sought by one or more of the Fighting Services, by the Ministry of Health, or by other Government departments. On problems such as malaria, typhus, and the testing of insecticides and insect repellants, the Council's wartime programme was closely integrated with those carried out by workers in the Dominions and the United States of America, so as to prevent undesirable overlap.

MALARIA

Experience during previous wars had shown that malaria may constitute so serious a menace to the health of troops engaged in operations in areas where the disease is endemic as even to endanger the success of a campaign. In the war of 1914-18, under static conditions, it was sometimes possible to obtain a satisfactory degree of control of malaria by methods directed against the mosquito larvae, but in mobile warfare and in certain types of country such methods were of limited application. The prophylactic use of quinine did not prevent the incidence of malaria; efficient mosquito repellents had not been developed. and it was impracticable to give the individual complete protection against infection.

In the years between the wars, an important advance was made in the chemotherapy of malaria by the introduction in Germany of the synthetic drugs " Plasmochin " and " Atebrin ". Combined treatment with quinine and " Plasmochin " was soon afterwards reported to be highly effective in the cure of relapsing malaria, but these reports were not universally accepted:

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moreover, owing to the toxicity of " Plasmochin ", the treatment had to be carried out under careful supervision in hospital and it could not be used under field conditions; accordingly, this method was not generally adopted. " Atebrin " was found to be effective in the treatment of the malarial attack, but its advantages and disadvantages compared with quinine were in those days a matter of dispute.

In this country an extensive programme of research aimed at the production of new antimalarial drugs, and studies of their mode of action, had been in progress under the aegis of the Council's Chemotherapy Committee since 1929, and during the war this work was continued. At the Molteno Institute, Cambridge, directed by Professor D. Keilin, Dr. Ann Bishop of the Council's staff and her colleagues were engaged in testing new synthetic compounds for activity in experimental malaria infections (p. 311). These compounds were prepared by chemists working on behalf of the Chemotherapy Committee in different parts of the country, and many of them were synthesised at the National Institute for Medical Research by Dr. H. King and his co-workers. An account of the war-time researches on malaria at the National Institute by Dr. King, Dr. Hawking and others is given on pp. 217-8. As part of the scheme of work sponsored by the Chemotherapy Committee, fundamental studies of the mode of action of quinine and other antimalarial drugs had been made before the war by Sir Rickard Christophers and Dr. J. D. Fulton at the London School of Hygiene and Tropical Medicine, with support generously provided, through the Council, by the Trustees of the late Viscount Leverhulme.

While many of the studies of new antimalarial drugs in progress in the United Kingdom already showed considerable promise by the spring of 1939, it was imperative, as a short-term measure, to ensure that this country was adequately supplied during the period of hostilities with antimalarial drugs of which the value was already firmly or partly established. Emergency steps were therefore taken to arrange for the manufacture here of British equivalents of the German drugs " Atebrin " and " Plasmochin " (see also p. 73); the drugs were manufactured in Britain under the non-proprietary names of mepacrine and pamaquin. Tests carried out early in the war by Dr. Fulton at the Liverpool School of Tropical Medicine (p. 336) confirmed that the British-made drugs were identical in action and toxicity with their German prototypes.

In 1941, when Pearl Harbor was attacked by the Japanese, fighting extended rapidly over the malarious countries of the Far East. The fall, in 1942, of the Dutch East Indies, involving the loss of 95 per cent. of the world supply of cinchona bark, converted the threat of a quinine shortage to an immediate and desperate reality and emphasised the urgent need for alternative drugs for the prevention and treatment of malaria. The primary requirement was a true causal prophylactic or, failing that, a drug having effective suppressive value under the conditions in which it could be used by the forces in the field. Accordingly, although the Allied Nations had only a relatively limited experience of " Atebrin " therapy up to that time, the important decision was taken that mepacrine should be manufactured here on a very large scale. This expanded production of mepacrine eventually more than compensated for the loss of quinine from the Dutch East Indies. In addition to the home production of mepacrine, the technical details of its manufacture—worked out in this country—were made available to American firms.

With a view to the possible development of still better antimalarial drugs than mepacrine and pamaquin, it was realised that a closely integrated effort was required, in which academic laboratories and manufacturing firms with

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a special interest in the chemotherapy of malaria could collaborate freely. At the instigation of the Council, therefore, a conference was arranged, in March, 1943 between representatives of the Council, the Therapeutic Research Corporation of Great Britain and Imperial Chemical (Pharmaceuticals) Ltd. A joint programme of research, based on important discoveries already made in the Imperial Chemical (Pharmaceuticals) Laboratories which culminated later in the development of the highly effective new drug " Paludrine " (see below), was then worked out by a panel of the Council's Chemotherapy Committee and representatives of the firm. At the same time, there was established a regular interchange of confidential information on antimalarial drugs between the groups of workers in academic and commercial laboratories in Great Britain and the United States, through the agency of the Medical Research Council on the one hand and the Committee on Medical Research of the Office of Scientific Research and Development (U.S.A.) on the other. Some of the subsequent developments in wartime work on antimalarials with which British and Dominion workers were largely concerned are discussed in the following paragraphs.

The Origin and Work of the Malaria Committee

In August, 1943, the Council appointed a Malaria Committee (p. 416), under the Chairmanship of Major-General (now Sir Alexander) Biggam, with the purpose of assisting the Armed Forces in the control of malaria. The Committee was composed of representatives of the Fighting Services and of academic workers interested in malaria, pharmacology, entomology and chemistry. Its terms of reference were " to advise and assist on any matters concerning scientific research in the problems of malaria control."

In practice, the Committee concerned itself especially with the clinical aspects of malaria, including individual prophylaxis, and, in view of the limited scientific man-power and other resources available in 1943, it was decided that its research programme should be confined to work which was likely to be of practical importance to the Armed Forces before the end of the war (expected in 1947, at the latest).

At the time of the Committee's appointment, mepacrine was already available as a possible substitute for quinine, but—as indicated above—its relative merits and disadvantages were subjects of dispute, and there had been no experience in giving it to large numbers of Europeans over long periods. The prophylactic use of mepacrine on a large scale for the protection of the Combined Forces in North Africa was initiated in 1943. The dose used was 0.2 g. twice weekly; this dosage of the German equivalent, " Atebrin," had seemed satisfactory in small-scale trials among native plantation labour in Malaya before the war. The first two doses were taken by the men of the First Army without ill effect, but the third and fourth doses provoked severe gastro-intestinal and other disturbances, which incapacitated up to 25 per cent. of the men in some Units. These toxic disturbances were so pronounced, and so unexpected, that it was decided by the Army authorities to set up a special Malaria Research Unit, as part of the Directorate of Biological Research, War Office, to investigate the toxic effects which might follow the use of mepacrine, and to see how these could be avoided.

The staff of the Army Malaria Research Unit eventually consisted of:— Lieut.-Col. B. G. Maegraith (Director), Dr. R. E. Harvard, Majors G. M. Brown, W. H. Dalton, A. Kirshner, R. J. Rossiter, Captains K. N. Irvine, J. C. Lees, D. S. Parsons, C. N. Partington and J. L. Rennie. The Unit was stationed at Oxford, in the various laboratories of the University. Over 200 students and certain men from Army Units volunteered to assist in these

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experiments, by taking mepacrine over long periods and by permitting detailed laboratory investigations. The Unit was disbanded in December, 1944.

Other investigations were started at the Royal Army Medical College, Millbank, London, under the direction of Lieut.-Col. W. R. M. Drew and Major J. Reid, to ascertain whether men who had taken mepacrine for long periods in West Africa showed any evidence of toxic effects on the liver or kidneys.

At its first meeting the Malaria Committee formed a number of sub-committees to give detailed attention to different aspects of its work; other sub-committees were formed later. The most important of these *ad hoc* bodies were:—the Pharmacological and Chemical, the Therapy, the Drug-Prophylaxis, the Combat-Area-Prophylaxis and the Standardisation of Nomenclature and Procedures Sub-committees.

Close collaboration was maintained between the different sub-committees, and subjects were shared between them as circumstances dictated; the majority of their activities can therefore be considered together.

Pharmacology, chemistry and drug-prophylaxis.—The attention of the Pharmacological and Chemical Sub-committee was directed chiefly to the study of the pharmacology and toxicity of mepacrine. In the early days, in particular, attempts were made to explain the acute reactions which had followed the use of mepacrine in North Africa. Parallel studies made in Britain and the United States indicated that reactions following the giving of mepacrine were due not to contaminants or to deterioration, but to the drug itself. Mepacrine exerts a direct irritant action on the alimentary canal which can be demonstrated in dogs or, by X-rays, in men; but this effect is produced only by large doses, and it did not seem to be the explanation of the untoward results experienced in North Africa. It was found that of all the different systems of taking mepacrine prophylactically, division into two half-weekly doses was the schedule most likely to provoke toxic reactions. The reactions occurred particularly at the third or fourth dose, that is between the tenth and fourteenth days. If the recipients persisted in taking mepacrine, they soon became tolerant and suffered no further disturbances. The time of occurrence of the symptoms suggested that the men became sensitised to the drug and subsequently they became desensitised; this hypothesis, however, was never clearly proved. In particular the geographical distribution of the toxic disturbances was very puzzling, for they were very conspicuous in the Western half of the Mediterranean, but they were absent from the Eastern half, among troops under apparently the same regime of administration. On the practical side, it was found that if men took 0.1 g. mepacrine daily, such toxic disturbances did not occur. After 1943, this type of toxic disturbance caused no more trouble. During the course of this work, the effects of acute over dosage of mepacrine were studied in volunteers; toxic reactions were found to be exacerbated by restriction of fluid intake. The chronic toxicity of mepacrine was studied at Oxford and at Millbank, and it was shown that men could take 0.7 g. weekly, for long periods, without any resultant toxic effects on the liver or other organs.

Workers in America, particularly Dr. J. A. Shannon and his colleagues, had developed methods for the estimation of mepacrine in blood and plasma. These methods were studied and applied in Britain, being adapted to the apparatus which was available. In addition, simplified field methods were developed (by Professor E. J. King and by Dr. J. Yudkin) for estimating the mepacrine in blood and in urine. It was shown (by the Army Malaria Research Unit) that, in certain circumstances, the concentration of mepacrine in the plasma could be computed from the amounts of the drug and of ammonia in the urine. Field trials of these methods were undertaken in Italy by Major G. M. Brown and Captain J. L. Rennie in 1944-5.

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The American workers had also shown that mepacrine is at first stored in the tissues, and that with a daily dose of 0.1 g. the maximal plasma concentration is not reached until about six weeks after the start of therapy. Degradation and excretion similarly take place slowly. These findings were confirmed and extended at Oxford and at Millbank, and investigations were directed to the discovery of whether there is any alteration in the absorption and speed of degradation of mepacrine in men who have taken the drug for long periods. The degradation products of mepacrine were studied by Mr. D. Ll. Hammick and by Professor E. J. King; one of the products excreted in urine was shown to be 2-hydroxy-6-chloro-9-aminoacridine.

At the end of 1943, important new experiments in drug prophylaxis against malaria were carried out by Major K. Mellanby, Dr. W. D. Nicol, Major J. Reid, and Mr. P. G. Shute. Thirty-two volunteers were given 0.1 g. mepacrine daily for some time before, and for two to three weeks after, exposure to the bites of mosquitoes infected with malignant tertian malaria. Only one of these persons developed malaria, showing that mepacrine is very efficient in preventing overt clinical attacks of this disease. Further work showed that the suppression of malaria depends on the presence of an adequate concentration of mepacrine in the blood at the time when clinical attack might be expected to appear, rather than at the time of infection. Subsequent tests by Major Reid and Mr. Shute showed that certain new drugs, e.g., SN 6911 (" Sontoquin ") and compound 4430 (*vide infra*), had a similar action. All this work depended upon the skill of Mr. Shute in breeding and infecting mosquitoes in the large numbers required.

To determine whether the incidence of malaria among troops taking mepacrine as a suppressive was due to inadequacy of the method or to failure to take the prescribed dosage, special teams were sent in 1943 to malarious districts near and in the combat areas of Italy. As a result of this survey, it seemed clear that the incidence of malaria was due not to inadequacy of the methods of prophylaxis but to failure in their observance. Stricter supervision of prophylactic measures (especially of the daily administration of mepacrine) was enforced, and the incidence of malaria in the later stages of the war was strikingly reduced.

Therapy.—With the collaboration of medical officers attached to the Forces, comparative trials were arranged for various courses of mepacrine in parallel with the standard course of quinine, mepacrine and pamaquin. These trials showed that mepacrine was as effective as quinine in the treatment of malaria, provided that large " loading " doses were given in the first few days. However, none of the treatments in general use was effective in preventing relapses following infection by *P. vivax*. Work between the two world wars had suggested that pamaquin is useful in preventing these recurring attacks, but—as pointed out on p. 57—the evidence for this claim had not been generally accepted. Accordingly, special trials were arranged at Colchester Military Hospital, 107 General Hospital, Oxford, 73 General Hospital, Hatfield, and the R.A.F. Hospital, Halton, at first under Major W. Kelleher and Major K. S. Thompson, later under Major R. O. C. Johnstone and other officers. The results of treatment with a combined course of quinine and pamaquin were compared with those following a standard course of mepacrine, using alternate cases; records were maintained for more than five months after the cessation of treatment. Of the men treated with mepacrine alone, 34 per cent. relapsed; of the men treated with quinine and pamaquin only 10 per cent. relapsed. This decisive evidence of the value of pamaquin (obtained under statistically satisfactory conditions) stimulated renewed attention to

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pamaquin, and led to extensive re-investigations in America of the 8-amino-quinoline series of compounds.

At the beginning of 1944, the Malaria Committee was informed of the development of various promising new antimalarial compounds by Curd, Davey, Rose and their colleagues in the Manchester laboratories of Imperial Chemical (Pharmaceuticals) Ltd. These compounds had received preliminary clinical trials by Dr. A. R. D. Adams of the Liverpool School of Tropical Medicine. The first of them, No. 3349, was given a clinical trial at Colchester, but although it was active against human malaria, it was not as effective as mepacrine. Trials were later given to compound 4430 which was much more hopeful, and finally compound 4888 was examined. This compound (N^1-*p*-chlorophenyl-N^5-isopropylbiguanide), which is now named "Paludrine", has many advantages over mepacrine and quinine, and it may indeed prove to be the best antimalarial drug for general use. The original clinical trials and study of its pharmacology in man were carried out by Dr. A. R. D. Adams and Professor (then Lieut.-Colonel) B. G. Maegraith; and many other workers have assisted in its further clinical evaluation. With the dissolution of the Malaria Committee in 1946, further investigations on "Paludrine" by field trials and other methods, will be co-ordinated by the Malaria Sub-committee of the Colonial Medical Research Committee, recently set up jointly by the Council and the Colonial Office.

Standardisation of nomenclature and procedures.—In the early work of the Malaria Committee much confusion was caused by differences in meaning attached to certain terms commonly used in malariology. Definitions were, therefore, sought for the more important of these terms. Although complete agreement was not reached by clinicians, parasitologists and other interested groups of workers, misunderstandings were cleared away and the importance of each worker carefully defining his terminology was emphasised. Similar useful work was accomplished towards the standardisation of the procedures to be employed in the clinical evaluation of new antimalarial compounds.

During the whole period of its work the Malaria Committee maintained close contact with the American Board for the Co-ordination of Malarial Studies, and there was a prompt interchange of all reports and papers between the two bodies. In the early part of 1945 the Committee welcomed a visit from two representatives of the American body, Dr. R. Loeb and Dr. J. A. Shannon, and at the end of the year the Secretary and Assistant Secretary of the Council's Malaria Committee (Dr. F. Hawking and Major J. Reid) were able to pay a return visit.

In the above account of the Committee's work on malaria, various names have been mentioned in connection with specific problems. In addition, special mention should be made of the late Colonel S. P. James, F.R.S., whose wide knowledge and enthusiasm were a source of inspiration at all stages of the work, and of Brigadier J. A. Sinton, V.C., F.R.S., consulting malariologist to the Army, whose great experience and keen criticism were of constant benefit. In the investigations on the therapy and drug-prophylaxis of malaria much very valuable co-operation was received from Brigadier N. Hamilton Fairley and his colleagues at the Australian Army Medical Research Unit, Cairns, Queensland. Brigadier G. M. Findlay, Major J. Innes, and other investigators overseas also gave their help. Grateful acknowledgment must be made to the valuable contributions made by many other workers, whom it is not possible to name individually. Finally a tribute must be paid to the many volunteers who rendered possible much of the work at Oxford and at Millbank.

The two outstanding contributions of medical research on malaria during the war period have been the effective introduction of malaria suppression

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by mepacrine, and the synthesis by British workers of " Paludrine." The former was strategically decisive in the overthrow of Japan, permitting military operations to be conducted successfully in hyperendemic malaria areas; the latter, in that it is a true causal prophylactic in *P. falciparum* malaria and a partial prophylactic in *P. vivax* malaria, has led to a great advance in the therapy of malaria. The vast potential importance of DDT (p. 71) as an insecticide and larvicide in malaria control must also be recognised.

The final effect which these discoveries will have on the control of malaria under peacetime conditions is not yet known; undoubtedly, it will be far-reaching.

THE TYPHUS FEVERS

Louse-borne Epidemic Typhus

Experiences in the war of 1914-1918, and in the years following it, suggested the likelihood of extensive outbreaks of louse-borne epidemic typhus during the recent war. Accordingly, laboratory study of the disease was one of the major wartime activities at the National Institute for Medical Research (see p. 211). The workers there were in constant touch with workers in the Army Medical Service, particularly those at the R.A.M.C. Emergency Vaccine Laboratory at Tidworth, and later at Everleigh, Wiltshire. In Britain, attention was concentrated on those aspects which were not already being intensively studied in Canada and the United States. No research was therefore undertaken into methods of large-scale production of epidemic typhus vaccines: work was, however, carried out on methods of assaying such vaccines, and on comparing typhus strains from various parts of the world with a view to ascertaining whether the existing vaccines were likely to be effective wherever they were used.

Particular attention was paid at the National Institute to the chemotherapy of typhus, for no drug with specific therapeutic value against this infection was known at that time. After many compounds from various sources had been examined in vain for activity against the causal rickettsiae, two were found which were highly effective in experimental typhus in mice; these were *para*-sulphonamidobenzamidine hydrochloride (designated V147) and *para*-sulphonamidobenzamidoxime hydrochloride (designated V186). As these compounds were found to have no excessive toxicity for animals or human volunteers, it was considered justifiable to try them in cases of typhus in man. Accordingly, in June, 1943, with the co-operation of the Director-General, Army Medical Services, a British Army Typhus Research Team was constituted to carry out clinical trials with the new sulphonamides. The team consisted of Major (now Professor) M. van den Ende, R.A.M.C., Major (now Professor) C. H. Stuart-Harris, R.A.M.C., the former a member of the Council's scientific staff and the latter an attached worker at the National Institute for Medical Research, Major M. H. Gleeson White, R.A.M.C., and Captain W. L. Hawley, M.C., A.U.S., who was seconded to the team by the Director of Medical Services, European Theatre of Operations, United States Army; a number of other British Army Medical Officers assisted the Typhus Team. The first trials were carried out in civil hospitals in Algiers during the summer of 1943. Earlier in the year a few cases of epidemic typhus had occurred in Naples; with the beginning of winter the number of cases notified began to rise, until, in December, there was a sudden and serious increase in the incidence of the disease. The Typhus Team moved to Naples in January, 1944, and there carried out further trials of V147 and V186 until the epidemic began to wane. A full account of this work, together with a description of important studies in the immunology of typhus fever, has been

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published in the Council's *Special Report Series* No. 255. In the event, V147 and V186 failed to fulfil the hopes raised by their efficacy in mice; they proved of no practical value in human infections under field conditions. Their highly specific activity against rickettsiae is, however, of great scientific interest, as representing one of the few instances in which it has proved possible to inhibit the growth of intracellular parasites without damage to the host; this has an obvious bearing on the closely related and difficult problem of chemotherapy in virus diseases.

In November, 1943, at the request of the War Office, the Council appointed a Typhus Research Committee, of which Major-General L. T. Poole, then Director of Pathology, Army Medical Services, was Chairman, and of which the full membership is given on p. 416. One of this Committee's chief duties was to co-ordinate the research already in progress at the National Institute with that sponsored by the Army, and to secure close liaison with workers in the United States and the Dominions; at the time of its appointment, research on typhus was hampered by the conditions of secrecy imposed on such work. The Committee attempted, therefore, both by personal contact and by the circulation of memoranda to ensure that cognate unpublished material reached the interested investigators among the Allied Nations as quickly as possible. At first the Committee was wholly concerned with louse-borne typhus. Work on vaccines for this disease, and on the new delousing powders (p. 71), was in an advanced stage of development, and the Typhus Research Team was already established in North Africa when, in December, 1943, the work of the Committee was greatly extended, following an urgent request from South-East Asia Command, for assistance in combating serious outbreaks of scrub typhus that had appeared among the troops in Burma.

Mite-borne Scrub Typhus

Scrub typhus has long been known as a disease of Japan and China. It is due to inoculation with *Rickettsia tsutsugamushi* by the agency of larval Trombiculid mites; the latter, which are found in large numbers on the ground vegetation in certain areas, feed predominantly on small rodents, particularly rats. In 1924, workers at the Institute for Medical Research, Kuala Lumpur, first identified the disease in Malaya, and it has since been recorded from Assam, Burma, parts of India, Ceylon, New Guinea, Queensland and a number of other places in the Far East.

When the imminence of war with Japan necessitated the despatch of British forces to Burma and Malaya, the menace of this jungle form of typhus fever was realised. In December, 1941, at a conference held in London between representatives of the War Office and the Medical Research Council, and Colonel C. H. Kellaway, Director of Pathology, Australian Army, decisions were taken that resulted in Dr. R. Lewthwaite, of the Colonial Medical Service and at the time Senior Pathologist, Institute for Medical Research, Kuala Lumpur, being flown from Singapore to Melbourne to work on the preparation of a vaccine against scrub typhus.

When the appeal from South-East Asia Command was received in December, 1943, no success had been achieved, either in Australia or America, in the preparation of an effective vaccine. The Typhus Research Committee recommended, therefore, that fresh work on scrub typhus vaccine should be initiated at the National Institute, by a method based on the growth of typhus rickettsiae in the lungs of mice. This work, which eventually led to the preparation, from the lungs of cotton rats, of a vaccine of high rickettsial content is discussed on pp. 66 and 213. Arrangements were also made for Dr. Lewthwaite to return to England for consultation, and Squadron-Leader C.

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Radford, an authority on mites, was despatched to an Army entomoligical unit in South-East Asia Command to study the ecology of the mite vectors. In addition, limited supplies of the mite-repellents, dibutyl- and dimethyl-phthalate, which had proved valuable in the hands of Australian and American workers in New Guinea, were sent to the Burma theatre for further trial.

In the spring of 1944 it was decided that Dr. Lewthwaite, temporarily seconded to the service of the War Office, should proceed to South-East Asia Command, to act as Field Director of a Medical Research Council Scrub Typhus Commission, to which Dr. K. Mellanby, released from the Army to the Council's service, and Squadron Leader C. D. Radford, R.A.F.V.R., were also appointed. The Commission's terms of reference were to review the information available and to define the extent of the scrub typhus problem; to advise the Supreme Allied Commander, South-East Asia, and the General Officer Commanding-in-Chief, India, on the practical measures which could be taken for its solution, having regard to operational requirements; to co-ordinate, where necessary, research on scrub typhus in India and South-East Asia Command; and to ensure that workers in the affected areas were kept informed of developments elsewhere.

The Work of the Scrub Typhus Commission

The Commission reached the Headquarters of the Supreme Commander, South-East Asia, in July 1944. Doubt as to the exact identity of the disease affecting the allied troops had already been dispelled by the isolation of the causal organism, *Rickettsia tsutsugamushi*, from human cases by Major M. T. Parker, R.A.M.C., and field work by members of the Commission in infected areas as widely separated as Imphal in Assam and Addu Atoll in the Indian Ocean repeatedly confirmed the presence on jungle rodents of the known Malayan vector mite, *Trombicula deliensis;* some of these mites yielded strains of *R. tsutsugamushi*.

With a view to extending knowledge of the epidemiology of the disease, a field laboratory, under the military command of Lieut.-Colonel J. R. Audy, R.A.M.C., was established at Imphal. Here Dr. K. Mellanby and others carried out detailed studies of the mites, their mammalian hosts, the botanical associations in infected areas, and other factors of importance in scrub typhus. A field research team of the Medical Directorate, G.H.Q. India, under Major S. L. Kalra, I.A.M.C., collaborated in the inquiries. A report on the work of the laboratory, which has important peacetime implications, is being prepared for publication.

Meanwhile the Commission began an active campaign to reduce the incidence of the disease, which had reached alarming proportions. In the period July-October, 1944, 3,000 cases occurred in Fourteenth Army alone, with a mortality of 5 to 20 per cent., and there was the prospect that much larger forces would soon be deployed in infected areas. Furthermore, ignorance of the rôle of the mite had lent an air of mystery to the outbreaks, so that the troops at risk were unduly alarmed. An immediate requirement was to dispel their exaggerated fears by instruction both on the cause of the disease and on the means of prevention. With these objects in view, a film showing the life-history of the mite, its habitat, the technique of certain counter-measures, and other relevant features, was made under the technical direction of Dr. Mellanby; the anti-malarial organisations were utilised to disseminate information about preventive measures, and frequent interviews and lectures were given with the same purpose. Measures against rats, the common animal reservoir of the disease and host of the mite, were unlikely to prove effective under active service conditions, so special attention was directed towards anti-mite precautions. These involved principally the improvement of camp sites

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so as to make them unfavourable to mites, and the use of protective clothing and mite-repellents. With regard to the latter, Dr. Mellanby and Squadron Leader Radford visited Dr. R. N. McCulloch in Australia, and also American workers in New Guinea, to obtain first hand information of the field use of dibutyl- and dimethyl-phthalate. For practical reasons the method of McCulloch, using dibutyl-phthalate, was considered the more suitable under the conditions pertaining in South East Asia Command, and the troops were instructed accordingly.

In June, 1944, Dr. Forrest Fulton reported to the Typhus Research Committee that the vaccine against scrub typhus on which work had been progressing at the National Institute gave a fair degree of protection to mice (see p. 213). A limited field trial of the vaccine was begun in the autumn, small amounts being despatched to Dr. Lewthwaite for the inoculation of selected Army units. Before any answer as to the efficiency of the vaccine in man had been obtained, an urgent request was received from South East Asia Command in November, 1944, for one and a half million doses of the vaccine, the dead-line date for the first 100,000 doses being fixed for August, 1945. In spite of the lack of positive scientific evidence of protection in man, the Army authorities decided that, in view of the very large numbers of troops involved and the possibility that the vaccine might save lives, its mass production should be undertaken. As described on p. 17, large quantities of the vaccine were prepared by the Wellcome Foundation for the Ministry of Supply, and as the material became available it was sent to Headquarters, Allied Land Forces, South East Asia Command. The sudden end of the war against Japan prevented the assessment by the Army of the efficiency of the vaccine. However, since the war, Dr. Lewthwaite has organised further field trials of the vaccine among civilian populations, and the results of these, when available, should be of great interest.

INFECTIVE HEPATITIS AND SERUM JAUNDICE

The Origin and Work of the Jaundice Committee

Outbreaks of jaundice among Service personnel were so frequent in the recent war as to constitute a serious drain on manpower. Among the British troops in the Mediterranean area there were 4,000 cases of jaundice in 1941-42, and 12,000 in 1942-43. A large-scale outbreak occurred among the American troops who were arriving in Northern Ireland in 1942; this particular outbreak was afterwards shown to have been due to the inoculation of the troops with virus-contaminated yellow fever vaccine. About the same time, it became apparent that jaundice was also an important problem in clinics for the treatment of venereal disease. These events gave rise to anxiety over the possibility of even larger epidemics in the Services and of the spread of the disease to the civilian population; towards the end of 1942, therefore, the Ministry of Health asked the Council's help in dealing with the situation. Informal conferences were held in January, 1943, which eventually led to the formation of the Council's Jaundice Committee (p. 417) and Jaundice Research Team. The Jaundice Committee decided that in view of the shortage of highly trained bacteriologists and epidemiologists, and the difficulty of obtaining suitable laboratory facilities and experimental animals overseas, it would be best to concentrate work on the disease in this country. Additional reasons were the undesirability of carrying out transmission experiments in epidemic areas and the greater number of human volunteer subjects available in the United Kingdom.

A team was therefore formed, under the general direction of Professor S. P. Bedson, consisting of a bacteriologist (Dr. F. O. MacCallum), a biochemist (Dr. M. R. Pollock), a clinician (Dr., later Major, Clifford Wilson), a

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clinical pathologist (Captain J. A. R. Miles) and an epidemiologist (Dr. A. M. McFarlan). The team was housed in the Department of Pathology, University of Cambridge, and eventually jaundice was made notifiable in Civil Defence Region IV, which includes Cambridge and has a population of 2,650,000. Under this arrangement there was no shortage of clinical material for study (see also p. 175). The Jaundice Committee also established contact with the many other workers in this country and America who were engaged on cognate researches.

In the early years of the war a number of different forms of jaundice were recognised which produced similar clinical and morbid anatomical appearances. These were sporadic catarrhal jaundice at home, epidemic jaundice at home, epidemic jaundice overseas, post-vaccinal jaundice, homologous serum jaundice and post-arsenical jaundice. As a result of the work sponsored by the Jaundice Committee, as well as studies carried out by other workers in this country and abroad, it is now known that the first three are identical and constitute "infective hepatitis"; the second three are identical and constitute "homologous serum jaundice." Both these diseases are due to a virus, but there are clinical differences between them, and there is reason to believe that the two viruses are distinct, though probably related, on the analogy of the influenza viruses A and B. The establishment of the aetiology of homologous serum jaundice was not easy, owing to the unusually long incubation period, and its successful achievement was an outstanding event in the medical history of the war. It is now appreciated that jaundice has commonly been the result of therapeutic procedures, particularly the use of inadequately sterilised syringes to give injections, and the way is open for the abolition of jaundice in V.D. clinics and other medical departments in which numerous injections are given or blood samples are taken (see p. 196). It has also been established that the transfusion of whole blood carries little risk of homologous serum jaundice. The elimination of the infective agent from human serum or plasma for therapeutic purposes is more difficult (p. 191), but as only relatively few sera contain the icterogenic virus, the risks should be reduced by the avoidance of large-scale pooling; this argument is supported by the extreme rarity of jaundice after transfusion of whole blood, where pooling is not practised.

The investigation of infective hepatitis proved most arduous. Many species of animals were used, as well as every procedure known by pathologists to increase susceptibility to viruses, but, in spite of some promising results, transmission to animals has not yet been achieved with certainty. It was therefore necessary to use human volunteers. These were not easy to find in a time of total war, because the incubation period of infective hepatitis and the duration of illness are both long, and the experimental production of jaundice is not free from risk both to the individual and to the community. Although a small number of conscientious objectors volunteered for transmission experiments, the major source of supply was constituted by patients with rheumatoid arthritis. It was already known that the symptoms of rheumatoid arthritis are sometimes relieved by an attack of jaundice, and patients were therefore invited to volunteer with the twin objects of discovering whether jaundice could be transmitted, and whether jaundice so induced would in fact relieve rheumatoid arthritis. In all, some 400 volunteers were inoculated, of whom 350 were patients with rheumatoid arthritis, and jaundice developed in about 10 per cent. It was confirmed that the signs and symptoms of rheumatoid arthritis were often much relieved by an attack of jaundice, but the remission was unfortunately only temporary. Though jaundice is a useful research "tool" for the study of rheumatoid arthritis, it was clear that it could not be recommended as

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an effective treatment, and the prospect of combining research on jaundice with the large-scale treatment of rheumatoid arthritis had to be abandoned.

The two most important discoveries made by the Council's Jaundice Team were that a virus is present in the blood in post-arsenical jaundice, and that virus is excreted in the faeces in infective hepatitis. Their whole series of observations, taken in conjunction with results obtained by research workers in America, West Africa and elsewhere, has given a consistent picture of the distribution of the virus in infective hepatitis and homologous serum jaundice, and of the probable routes of infection. The results support clinical and epidemiological observations to the effect that infective hepatitis may sometimes be an excremental disease, distributed by flies and water, though the opinion of the majority of workers in this country is that in most instances it is droplet spread. Attempts to develop a serological test for the presence of the infection were inconclusive. The difficulties due to lack of a susceptible animal must again be emphasised. Without such an animal it proved impossible to bring the research to the final goal of a prophylactic vaccine. Nevertheless, it should be mentioned here that American workers have had very promising results in the prevention of jaundice by the use of gamma globulin, a concentrate prepared from human plasma in the blood banks.

The clinical and epidemiological studies (see also p. 175) are of great interest to physicians and hygienists, though they are too extensive for summary here. Much of the epidemiological work was naturally carried out by the Services, but a close liaison was established between the workers at home and overseas, and the Jaundice Committee proved a valuable agency for assessing and diffusing information as it became available. Two striking phenomena in jaundice in the Services were the high attack rate in officers and flying personnel as compared with ordinary ranks and ground staff; and the low attack rate, but high mortality, in coloured troops. The former phenomenon remained unexplained, the latter may have been due in part of differences of diet. Assessment of various laboratory tests showed that Hunter's test for bile in the urine was of much value in the detection of latent cases, while the bromsulphthalein test and the erythrocyte sedimentation reaction might be valuable in diagnosis in the pre-icteric stage. Hepatic function tests are otherwise of little value in acute hepatitis. Biopsy of the liver is of much assistance in controlling research studies, though it is too dangerous to be used as a routine diagnostic test in these diseases.

The course of infective hepatitis and homologous serum jaundice was shown to be extremely variable. In order to test the value of a given line of treatment, a large sample of cases must be taken and an equally large number of controls. Objective criteria of comparability and of recovery are fairly easily established, but they demand long periods of observation. For these reasons the majority of the therapeutic trials were carried out in this country, as it was rarely practicable to secure adequate conditions overseas. Hope had been entertained that these acute diseases of the liver would be rapidly improved by diet or dietary principles, but the results of therapeutic trials carried out on strict statistical lines were, unfortunately, almost completely negative. There was no difference in response whether the protein or the fat content of the diet was high or low, nor was the value proven of lipotropic substances, such as methionine, choline and cystine, though there was a suggestion that cysteine had some therapeutic effect.

Accounts of some of the researches carried out by members of the Jaundice Research Team and their co-workers have already been published in the medical press. A further publication, in the Council's *Special Report Series*, is contemplated.

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TUBERCULOSIS

The Origin and Work of the Committee on Tuberculosis in Wartime

The Committee on Tuberculosis in Wartime (p. 417) was appointed by the Council at the request of the Ministry of Health, in the autumn of 1941; the Chairman was the late Viscount Dawson of Penn and the Secretary Dr. P. D'Arcy Hart of the Council's staff. During the first two years of the war, a reversal of the favourable pre-war trend of mortality from tuberculosis had already become apparent; the Committee was charged, therefore, " to assist in promoting an investigation of the extent and causes of the wartime increase in the incidence of tuberculosis, particularly among young women, and also to advise the Council regarding possible preventive measures ".

The Committee's report was published in 1942 as the Council's *Special Report Series* No. 246: its survey of the position, up to the early part of that year, showed that all age-groups had been involved to some extent in the increased mortality from tuberculosis; that the increase was common to both pulmonary and non-pulmonary forms, and that those affected included not only young women, as had been suspected, but also children and the older male age-groups. A particularly disturbing feature was the increased mortality of children from tuberculous meningitis. After a critical review of the available evidence, the Committee made a number of practical recommendations—in particular, the controlled use of mass radiography for the purpose of detecting latent dangerous sources of infection on the one hand and early cases in need of care and treatment on the other, and also various important measures of a public health and administrative nature. Many of these recommendations were rapidly implemented by the Ministry of Health, and their adoption may well have contributed to the gratifying fall in the general mortality rate from tuberculosis which occurred in the later years of the war.

Before routine mass radiography could be introduced by local authorities as a check to pulmonary tuberculosis, it was necessary that a standardised instrument of high quality should be available. The transportable sets ultimately sponsored by the Ministry of Health and the Department of Health for Scotland embodied the essential recommendations on design made by a technical sub-committee of the Council's Committee on Tuberculosis in Wartime; the sub-committee's findings were recorded in an appendix to the Committee's report. The first set to be produced was used for a pilot survey on selected civilian groups by a special Unit formed by the Council: the members of the Unit were Miss Kathleen C. Clark, of the staff of Ilford, Limited, Dr. D'Arcy Hart, Dr. Peter Kerley and Dr. B. C. Thompson. The objects of this investigation were to establish standard technical and administrative methods so as to assist those responsible for the national scheme; to estimate the incidence of tuberculosis during wartime in various civilian groups, and thus to assess the demands likely to be made on the tuberculosis services as a result of mass radiography; and to throw further light on the epidemiology of the disease. The survey took place during 1943, and it covered approximately 23,000 persons from two factories, a large office group and a mental hospital, all of which were in Greater London. The report of this work (*Spec. Rep. Ser.* No. 251) was issued by the Council in 1945; it is, in effect, a valuable guide to the administration and technique of civilian mass radiography, as well as containing the statistical results of the Unit's survey.

In view of the finding noted by the Committee on Tuberculosis in Wartime, that the increase in non-pulmonary tuberculosis during the first two years of

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the recent war had affected persons at all ages, and not merely children as in the first world war, the Council, in January, 1943, summoned a conference of experts to discuss the feasibility of determining whether this increase was due mainly to infection with the human or the bovine type of tubercle bacillus. Discussion revealed practical unanimity on the value of obtaining such information, and it was therefore decided to conduct a nation-wide survey of non-pulmonary tuberculosis with this object in view. In England, the inquiry was directed by Professor G. S. Wilson and Dr. D'Arcy Hart and was conducted by the Emergency Public Health Laboratory Service (see p. 171); in Wales the inquiry was directed by Professor W. H. Tytler and Dr. V. D. Allison; and in Scotland, by a Committee under the Chairmanship of Professor J. W. S. Blacklock.

The Murine Type of Tubercle Bacillus (the Vole Acid-fast Bacillus)

Another line of approach to the problem of controlling tuberculosis has been that of Dr. A. Q. Wells, who had grants from the Council before the war and is now a member of their scientific staff. In 1937 Dr. Wells isolated from voles an acid-fast bacillus of unusual interest. This differs in certain features from the human and bovine types of tubercle bacillus, and is now recognised as a third mammalian type—the " murine " type. Observations on guinea-pigs showed that infection with this organism conferred a significant degree of protection against subsequent inoculation with virulent human or bovine tubercle bacilli. The possibility arose, therefore, that the murine type of bacillus might be suitable for use as an immunising vaccine in man. Accordingly, Dr. Wells carried out an investigation on human subjects, the result of which was to show that living murine bacilli in suitable dosage could be inoculated by the multiple puncture method into the skin of tuberculin-negative reactors without giving rise to any general disturbance or to any serious local inflammation. Subjects inoculated in this way became tuberculin-positive as rapidly as after inoculation with the well-known B.C.G. vaccine. A full account of the work has been published in the Council's *Special Report Series* No. 259.

At a joint conference between representatives of the Prophit Committee of the Royal College of Physicians, the Ministry of Health and the Medical Research Council, it was recommended that a field trial to determine the comparative prophylactic value in man of the B.C.G. and of the vole bacillus should be organised when circumstances were favourable. Plans to this end are being considered. It seems likely that, to provide a clear answer, the trials would need to be made in a native or other population among which " negative tuberculin-reactors " are common, and in which the disease nevertheless presents a numerically serious problem.

PARASITIC AND BITING INSECTS

Louse Infestations

During the war of 1914-18, serious outbreaks of epidemic typhus, and the incidence of trench fever, led to much research on methods for controlling the responsible insect vector, the louse; but, in spite of the introduction of field delousing procedures, it never proved possible to eliminate the risk of these louse-borne infections, on account of the continual reinfestation that occurred; none of the chemicals used for destroying lice in that war gave protection for more than a couple of days. To achieve control, some insecticide with a lasting effect was required, with which undergarments could safely be treated.

With support from the Council, Professor P. A. Buxton undertook a programme of research directed towards the discovery of such an insecticide, and work was started early in 1940 in the Department of Entomology at

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the London School of Hygiene and Tropical Medicine. Dr. J. R. Busvine carried out trials with lethane preparations (thiocyanates) on infested tramps. It was found possible to keep the tramps virtually free from lice for as long as a month, even though associating with infested comrades, by impregnating seams in their undergarments with insecticide, provided the garments were not washed. To obviate this unhygienic condition, a lightweight body-belt, woven in such a way that it was covered with folds, was specially designed by the Cotton Research Board. When suitably impregnated with lethane, this body-belt proved efficient: it permitted the underclothes to be washed, but had the disadvantage that, if sweating were excessive, some skin irritation was liable to occur. In 1942, Professor Buxton organised successful large-scale trials of the "Lethane Belt" among native labour forces in the Eastern Mediterranean. At that time there was much epidemic typhus among civilians and in the labour corps; the belts were used on a large scale by the Army and reported on favourably. The troops themselves were almost free of lice, and military cases of typhus were very few and sporadic. In 1943, after the landing in Italy, the risk to the soldier was perhaps greater. By then, however, DDT powder was available in adequate amounts and the "Lethane Belt" was not needed. An important use for the lethane preparations in this country was based on their incorporation into a hair dressing which subsequently became known as "Lethane Hair Oil." The Ministry of Health instituted large-scale field trials of this mixture for the treatment of the head louse infestations which were, and still are, so common in girls in urban areas, and which proved troublesome among female factory employees during the difficult conditions of the war. The results of these trials were satisfactory, and the "Lethane Hair Oil" became a standard Ministry recommendation and was included in the National War Formulary.

While these studies on the lethane insecticides were in progress, other research on louse control was carried out in Professor Buxton's Department. Dr. W. A. L. David re-investigated the usefulness of fumigants for delousing. Hydrogen cyanide, which had been used during the 1914-18 war, was considered too dangerous for general adoption, and a wide range of newer and more satisfactory agents was tested, practical methods for their application in the field being developed. Dr. Busvine also re-examined the usefulness of physical methods (heat and cold) for the destruction of lice in clothing.

In December 1942, the Swiss firm Geigy, A.G. brought the possibilities of DDT (dichlor-diphenyl-trichlorethane) to the notice of entomologists in Britain and America. DDT had been first synthesised by Zeidler in 1874, but not until 1940 had its insecticidal properties been appreciated; since then it had been used in Switzerland on a limited scale against agricultural insect pests, house flies, etc. In Britain, Dr. Busvine examined the claims made for DDT as an agent against lice, and reported that it was clearly superior to any other known insecticide in this respect; its chemical stability and very low volatility, together with its relative safety to man, were a unique combination of desirable qualities. Early in 1943, Professor Buxton, as a member of the British Pyrethrum Mission which went to the United States to consider measures of economy in pyrethrum, was able to discuss the use of DDT with American entomologists. It was found that American workers had independently reached the same conclusions as Dr. Busvine with regard to DDT, and its large-scale production was agreed upon. One important advantage of DDT over lethane was that it is not readily washed out of impregnated garments. The part subsequently played by DDT in checking the Naples typhus epidemic is now well known, and, as a result of its use on impregnated garments, the troops engaged in the fighting on the Continent of Europe after "D-day" were kept virtually free of lice.

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Bed-Bug Infestation

In 1942 the Report of the Council's Committee on Bed-Bug Infestation (p. 417) was published (*Special Report Series* No. 245). This Report summarised five years' work, from 1935-40, sponsored by the Council at the request of the Ministry of Health, and it dealt with many aspects of the bed-bug problem. A special appendix was added to assist those responsible for the eradication of bed-bugs from air-raid shelters.

When DDT became available, the possibilities of bed-bug extermination were greatly enhanced, and research was undertaken to determine the best methods of using the material. Mrs. S. Barnes, working in Professor Buxton's Department with a grant from the Council, examined the residual toxicity of DDT films on surfaces such as cement, plaster, glass and woodwork. The use of distempers or paints containing DDT was investigated; but this method appeared to be unsatisfactory. During these investigations, close liaison was maintained with the Chief Scientific Adviser, Ministry of Works, particularly in regard to the performance of DDT on materials for prefabricated houses.

Scabies

Towards the end of 1940, the Ministry of Health made a grant for work on scabies by Dr. Kenneth Mellanby at the Sorby Research Institute, Sheffield. These funds were used to establish the Institute and to engage the services of up to twenty men, all conscientious objectors to military service, who were willing to serve as subjects for experiments on the transmission and prevention of scabies; these same volunteers later collaborated in important dietetic experiments, as mentioned on pp. 108 and 109. In the spring of 1942, the Council assumed financial responsibility for this work at Sheffield.

It was shown that scabies is usually transmitted by intimate personal contact and that transmission by fomites is a rare occurrence, the infective stage being the newly fertilised adult female *Sarcoptes*. As a result of this work, the disinfestation of bedding, a rather troublesome and expensive matter, has been given up by many progressive public health authorities, who now concentrate on the persons infested and on those who live in immediate contact with them.

As a result of studies of the parasite rate in scabetic subjects, it became clear that the course of the disease on initial infestation differed greatly from that on subsequent infestation. In a first attack, multiplication of the parasites progressed for about a month before the patient was aware of any symptoms. At about this time a true sensitisation developed, as judged by inoculation experiments, and itching became progressively more troublesome: the latter provoked scratching and consequent septic lesions of the skin. The combined effect of sepsis, scratching, and the host's immune reaction was to decimate the parasite population, which thereafter persisted at a low level unless the parasites were exterminated completely by treatment or, occasionally, by spontaneous cure. If a second infestation occurred, symptoms developed within 24 hours, due to the rapid re-activation of the host's immune reaction; in these subsequent attacks the parasite rate never reached the high levels recorded in primary infestations. It was also shown that re-infestation of cured cases was much more difficult to achieve than infestation of persons who had no immunity.

The various medicaments which have been used against scabies were critically tested, and observations were made of their actual effect on the mites in the skin. It was shown that, when properly applied, one treatment with benzyl benzoate emulsion would cure the disease in very nearly 100 per cent. of cases, and that disinfestation of clothing and bedding was unnecessary.

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IV

THERAPEUTICS, INCLUDING PENICILLIN

At the outbreak of the war of 1914-18, the state of preparedness in Great Britain in regard to the replacement of valuable drugs manufactured solely in Germany at the time was regrettably low. There developed very quickly, for example, a serious shortage of the German product " Salvarsan ", which was needed for the treatment of syphilis. To prevent similar difficulties in the recent war, Government action through the Committee of Imperial Defence, in regard to which the Council co-operated closely with the Ministry of Health, the Supply Board and other bodies, had been taken in advance to ensure the accumulation of adequate stocks of various natural and synthetic medicaments of foreign origin; the Secretary of the Council served on the relevant Committee of the Supply Board (Supply Committee VIII) and was Chairman of one of the two sub-committees between which its work was divided. Later, Supply Committee VIII became part of the organisation of the Ministry of Supply, and subsequently a Directorate of Medical Supplies was set up in that department.

In parallel with the arrangements made before the start of hostilities to ensure that this country had good stocks of various imported drugs, the Council, on behalf of the Committee of Imperial Defence, undertook the organisation in Great Britain of the large-scale manufacture and supply of certain antitoxins and other immunological products for which, under war conditions, there would be a heavy demand to meet expected Service and civilian needs; these arrangements are discussed further on p. 162.

To maintain a satisfactory supply throughout the war period of the more important synthetic drugs and diagnostic agents hitherto obtainable only from enemy countries, it was necessary to arrange for British equivalents of many of these compounds to be manufactured here, under Government licence where applicable; the Council, through Sir Edward Mellanby and later Sir Henry Dale, were largely concerned with these arrangements, which were made with the Association of British Chemical Manufacturers or, in appropriate cases, direct with individual firms. In some instances it was considered advisable to organise clinical trials of the British equivalents before they were issued for large-scale use; in others, the obvious chemical identity of the British substitute with its foreign prototype made special clinical trials unnecessary. A fundamental principle adopted was that the British equivalents should be manufactured and sold under non-proprietary names. Outstanding among the products tested clinically under this scheme were mepacrine and pamaquin as substitutes for the German " Atebrin " and " Plasmochin," respectively (p. 58): among others were bromethol for " Avertin," soluble hexobarbitone for " Evipan sodium," iodoxyl for " Uroselectan-B," pheniodol for " Biliselectan "; and pethidine: the last is the British equivalent of the German drug " Dolantin " or " Dolantol," which had been introduced just before the war as a synthetic substitute for morphine. The clinical tests of pethidine were sponsored mainly by the War Wounds Committee of the Council, and reference has been made to them on p. 42.

The arrangements for the manufacture and testing of these British-made equivalents of drugs of enemy origin were closely correlated with the activities of the Therapeutic Requirements Committee, as outlined overleaf.

Owing to difficulty in organising large-scale clinical trials, during the years 1939-45, of agents of general therapeutic interest, as opposed to those with a special wartime importance, the work of the Council's former Therapeutic Trials Committee was laregly in abeyance in that period. In 1940, however,

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this Committee arranged for limited clinical trials of the new synthetic oestrogen dienoestrol, which has since been introduced into medical practice.

During the war, many important investigations of new drugs of sulphonamide or sulphone type were made for the Council at the National Institute for Medical Research and elsewhere; these included examinations of the value of such drugs in anaerobic and other wound infections, in rickettsial diseases (p. 215) and in malaria (p. 218). Field tests of the prophylactic value of sulphonamides in rheumatic fever and some other conditions were also arranged, the most successful being the use of sulphonamide snuff (p. 179) to eliminate diphtheria bacilli from the noses of carriers of that infection. Accounts of the experimental and clinical trial of sulphonamides and other drugs in the prevention and treatment of infection in wounds and burns will be found in the relevant sections of this Report, pp. 34-37 and 43-46. Reference to the Council's *War Memorandum* on the medical use of sulphonamides is made on pp. 30, 35 and 77.

The Origin and Work of the Therapeutic Requirements Committee

As a result of the preparatory action taken by Government and other organisations, as outlined in the opening paragraphs above, considerable stocks of imported drugs and other therapeutic substances had been accumulated in this country before the war, but, when war was declared, it became a matter of urgency to ensure that these supplies were used economically and to the best advantage, and that satisfactory arrangements were made to maintain and augment them. Accordingly, in consultation with the Ministry of Health, the Council immediately appointed an expert Committee to advise on these questions in their bearing on medical treatment; subsequently, in consultation with the Ministry of Agriculture and Fisheries, it was agreed that veterinary applications of drugs should also come within the purview of the Committee. On the setting up of the Directorate of Medical Supplies in the Ministry of Supply, the Committee worked in close relationship with that body, as well as with the Ministries of Health and Agriculture, the British Pharmacopoeia Commission and the other bodies mentioned below.

The Committee first met, under the chairmanship of Professor L. J. Witts, on September 26th, 1939, with the title of the Drug Formulary Committee, but after consideration of the problems at issue it requested that its name should be changed to the Therapeutic Requirements Committee. There were already three bodies producing official drug formularies: the Pharmacopoeia Commission was responsible for the British Pharmacopoeia, the Pharmaceutical Society for the British Pharmaceutical Codex, and the Insurance Acts Committee of the British Medical Association for the National Formulary. What was necessary was a committee on which these three bodies would be represented, together with other members having expert knowledge of special subjects, so that the state of supplies and the changing needs of prescribers could be kept under constant review. This was the position occupied by the Therapeutic Requirements Committee, whose membership is given on p. 417, and of which Dr. C. H. Hampshire, the Secretary of the Pharmacopoeia Commission, served as Secretary.

Among its functions was to advise the controllers of the import and manufacture of drugs, as to which drugs were vitally necessary and must be supplied at all costs. It informed the medical and veterinary professions, and more particularly the key people responsible for the formularies, indents and quotas, which important drugs were scarce and must be used economically; it published

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the names of British equivalents for foreign drugs; it dealt with the problems which inevitably arise when any form of restriction is practised, and it indicated where exceptions should be made to avoid hardship.

The first business of the Committee was to prepare a list of drugs in common use, classifying them both as to therapeutic value and availability in wartime. In addition to the pharmacopoeias and other sources, the Committee made use of the list of medicines, chemicals and medical materials prepared by Supply Committee VIII (p. 73), the Ministry of Health schedules of drugs and dressings for the equipment of hospitals in the Emergency Hospital Scheme and for first-aid work, the list of British equivalents and alternatives for important foreign proprietary products compiled by the Association of British Chemical Manufacturers before the war, and the world survey of the countries of origin of drugs used in this country prepared by Mr. Arthur Mortimer, secretary of the Wholesale Drug Trade Association. A preliminary list was circulated in September, 1940, and in March, 1941, a revised list was published as the Council's *War Memorandum* No. 3, with the title " Economy in the Use of Drugs in Wartime ". These lists were at once adopted as a guide for the National War Formulary for use in the Emergency Medical Services, the Medical Services of the Fighting Forces and of the various Colonies, and for the assistance of the Import Licensing Department of the Board of Trade. Special lists were later prepared for other purposes, including " Aid to Russia " and " Post-war Relief ". The second edition of *War Memorandum* No. 3, issued in 1944, also contained an appendix on methods of disinfection, and on desirable measures of wartime economy in the use of bactericides.

Under an addition made in 1941 to the Defence Regulations, the Minister of Health and two Secretaries of State (acting respectively for Scotland and Northern Ireland) were empowered, after consultation with the Council, to make Orders, during the war, dealing with the replacement of scarce drugs by alternatives, and authorising chemists receiving prescriptions including scarce drugs to supply instead the alternatives named in the Orders, unless the doctor writing the prescription specified that no alternative was to be used. In fulfilling their statutory function in this matter the Council had the advice of the Therapeutic Requirements Committee. Shortages of drugs during the war were in part due to the armament programme. Alcohol, glycerin and mercury were required for munitions, and phenolic compounds for plastics. Other important drugs came under the control of the Ministry of Food and the Petroleum Board. Manufacture of drugs might be further restricted by shortages of labour and plant. In all such instances, steps had to be taken to ensure that the needs of medicine and veterinary science were properly estimated and adequately covered. Less controllable shortages were due to the difficulties of importation. This country had been dependent on supplies from overseas for a considerable proportion of its requirements of crude drugs, and of these imports a large proportion came from countries outside the British Empire. The civil war in Spain had led to a scarcity of ergot, which became intensified when Poland ceased to be a source of supply. The main source of such drugs as belladonna, digitalis, gentian, hyoscyamus, liquorice, stramonium and oil of dill was the Continent of Europe. This supply was at once reduced on the outbreak of war in 1939, and when France fell it was almost completely interrupted. In 1942 Japan overran the Dutch East Indies, thereby securing 95 per cent. of the world's cinchona production and leaving the United Nations with little more than a year's supply of quinine. (Details of the measures taken to meet the shortage of quinine will be found on p. 58 *et seq.*). Supplies of agar, so important in bacteriological work, were also cut off, as it was at that time almost a complete monopoly of the Japanese.

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These serious deficiencies had to be met by the suggestion of alternatives and substitutes, wherever possible, and the conservation of existing stocks for the purposes for which they were vitally necessary, as, for example, the limitation of quinine to the treatment of malaria. From time to time, notes dealing with these matters were prepared for publication in the medical and pharmaceutical press. Technical problems arising out of the need to store perishable drugs for unusual periods of time were reviewed. In addition, the Committee provided, as an appendix to the first edition of *War Memorandum* No. 3, a list of vegetable drugs, production of which within the Empire should be encouraged. The Ministry of Health thereupon formed a Vegetable Drugs Committee, which reported that the drugs in the list could be divided into two groups, a short-term group and a long-term group, and which pursued an energetic policy for the creation of supplies of the short-term group.

At the very beginning of the war, it became imperative to study means of conserving supplies of certain substances which, though widely prescribed, act as flavours or " vehicles " rather than as therapeutic agents. Examples are sugar, alcohol, glycerin, syrups, oils and fats. Reduction or omission of these materials meant a radical change in the prescription of medicines, and in the dressing of wounds and skin diseases. Tinctures gave place to tablets and watery extracts; tooth-pastes and cough mixtures acquired a wartime austerity. Ointments and creams were a particularly difficult group—owing to the shortage of glycerin, fats and starch, on the one hand, and, on the other, the much increased demand for anti-dermatitis creams, anti-gas ointments, burn dressings, sulphonamide pastes, mosquito repellents and applications for the treatment of parasitic infestations. One answer to the problem was to incorporate more water—in other words, to substitute creams for fatty ointments—but this was difficult because stocks of cetyl alcohol and other derivatives of sperm oil, which are favoured ingredients of creams, could not be replaced, until they could be manufactured synthetically, owing to the cessation of whaling expeditions. Many of the new synthetic materials for the manufacture of creams were of a proprietary nature, and far too little was known about their effects on the human skin and their power to take up medicaments in appropriate concentrations, to recommend their employment on a large scale. Although there was a flourishing cosmetic industry in Britain, it had been nobody's business to study the effects of the new synthetic bases and emulsions in a disinterested manner, or to publish the information with a view to the better prevention and treatment of diseases of the skin. Much was done by the Committee and related bodies—for example, by the introduction of the use of wool-wax, and by preventing the wasteful prescribing of vitamins in skin dressings. Nevertheless, the Committee was left with the feeling that the pharmacology of medicaments and bases to be applied to the skin had not hitherto attracted sufficient scientific interest, and the Committee's experience was similar to that of many others, in emphasising the need for long-term research on these problems after the war.

With regard to the work described above, the difficulties encountered were not essentially different from those of the 1914-1918 war, but an entirely new kind of problem was set by the rapid advance in chemotherapy which had begun in 1936. This is exemplified by the history of the sulphonamides, in which successive improvements due to research led through sulphanilamide, sulphapyridine and sulphathiazole to sulphadiazine and sulphadimethylpyrimidine, with the side developments of sulphaguanidine and succinylsulphathiazole. The problem was strictly comparable with the progressive improvement of aircraft and weapons of war, and it gave rise to the same difficulty in production programmes; sometimes there were special difficulties because of the need to obtain raw materials, such as calcium cyanamide, from abroad,

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Other examples of recent changes in therapy which gave rise to supply problems of varying degrees of complexity were the replacement of sulphur by benzyl benzoate in the treatment of scabies, the replacement of tannic acid by sulphonamides and penicillin in the treatment of burns, the sequence of safrol, lethane and finally DDT in the treatment of louse infestation, and the series thiourea, thiouracil and methyl thiouracil in the treatment of hyperthyroidism. Here it was the function of the Committee to warn the Ministry of Supply of impending changes, and at the same time to discourage mere fashions in prescribing which did not justify the cost of alterations in schedules. Much of the scientific work was naturally done by other committees, such as the Malaria Research Committee (p. 59) and the Chemotherapy Committee (p. 58), but the Therapeutic Requirements Committee formed a useful clearing house for information. The Council's *War Memorandum* No. 10 on " The Medical Use of Sulphonamides ", which was prepared by a large number of experts, on behalf of the Therapeutic Requirements Committee, was one of the most successful and widely read medical publications of the war, and it had a great effect, not merely in improving practice, but in popularising the new outlook on pharmacology, and in accelerating the acceptance of scientific standards in the control of treatment. The work of the Therapeutic Requirements Committee consisted essentially in the pooling and application of knowledge, and, apart from sponsoring certain *ad hoc* therapeutic trials, it did not engage directly in research. Nevertheless, a suggestion from the Committee that synthetic anti-malarial drugs should be examined for quinidine-like activity, owing to the exhaustion of stocks of quinidine, led to some unexpectedly interesting results.

The classification of drugs adopted by the Committee was sometimes criticised on the grounds that it failed to distinguish between the two separate considerations of whether a drug was " essential " and whether it was " available ". The justification is that the classification worked in practice. The Committee sometimes took a gloomier view of the future than events afterwards warranted, but this was certainly better than an over-optimistic outlook. With experience, the Committee came to appreciate the extent to which notification of shortages often increases demand, and that lack of one material increases the consumption of another: too rigid a classification and too tight a restriction, therefore, might actually increase the consumption of important drugs. In the end no dangerous shortages of essential drugs occurred, in spite of an increased total consumption of medicines during the war period.

The more permanent effects on prescribing produced by the Committee's activities during the war remain a subject for speculation. In general, they were the acceleration of changes which would have come more gradually in peace-time, an acceleration which was the result of expert direction and the avoidance of vested interests or unsupported tradition. Single substances and active principles were used instead of tinctures and mixtures; the many hospital pharmacopoeias, each with their favourite prescriptions, which are chiefly of historical interest, were replaced by the National War Formulary of the Ministry of Health, and the use of foreign or proprietary names was discouraged. Synthetic chemicals were substituted for galenical drugs. Bismuth salts gave way to magnesium trisilicate and aluminium hydroxide in the treatment of dyspepsia, boric lint was replaced by the sulphonamides and penicillin. Production of needless varieties of hypnotics and local anaesthetics was temporarily checked. Finally, as shown by the success of the memorandum on sulphonamides, a demand was created for disinterested accounts of the increasingly rapid developments and changes in pharmacology, and their scientific application to the practice of medicine,

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The Therapeutic Requirements Committee was discharged on the completion of its wartime task, most of its functions which are applicable to post-war conditions being taken over by the Drug Requirements Committee recently appointed by the Ministry of Health.

PENICILLIN

The History and Early Development of Penicillin Therapy

Pioneer Studies of Antibiotics: the Work of Fleming and Others

The investigations on penicillin at the Sir William Dunn School of Pathology, Oxford, were supported by the Council from the beginning of the work which led to the introduction of penicillin into medicine as a chemotherapeutic agent. In 1939, when the first application was made to the Council for assistance in developing a programme of research on penicillin and other antibiotics, the position was as follows:—

There had been recorded in the literature a large number of examples of mutual antagonism between different micro-organisms, and on more than one occasion attempts had been made to use this phenomenon as a basis for preparing therapeutic agents to combat infection. The most noteworthy and the most prolonged investigations, which were started at the beginning of the century, were devoted to the products of *Pseudomonas pyocyanea*. None of the attempts to use what are now called antibiotics had in the long run been successful.

In 1929, Professor (now Sir) Alexander Fleming, at St. Mary's Hospital, London, reported that as a result of an accidental contamination of a staphylococcal culture with a mould, he had observed dissolution of the staphylococci by some substance produced by the mould. He cultivated this fungus on broth and found that, after the fungus had grown for a few days, the broth was capable of preventing the growth of a number of pathogenic organisms, principally gram-positive—some of them even when the broth was diluted 800 times, though others were insusceptible. This broth he called " penicillin ", a name later to be applied to the inhibitory substance itself. It was shown that the broth was a slow acting type of antiseptic, and that 20 c.c. of it could be injected intravenously into a rabbit, and 0.5 c.c. intraperitoneally into a mouse, without producing more reaction than did uninoculated broth. Other experiments showed that the penicillin-broth was no more toxic than ordinary broth to leucocytes *in vitro*, and Fleming noted that this was the first antiseptic he had encountered which was considerably more harmful to bacteria than to tissue cells. He suggested that the broth might be a useful dressing to apply locally to infected tissues, and some patients were so treated. However, the results at that time were not sufficiently definite to stimulate further work. Fleming, writing in 1941, said in this connection:—

> " Prior to the second article cited (1931), a few tentative observations had been made on the effect of the local application of the unconcentrated culture to septic wounds (chiefly carbuncles and sinuses). Although the results were considered favourable there was no miraculous success. In those times septic wounds in the hospital wards were relatively uncommon, and it was not considered that the production of penicillin for the treatment of these was practicable, owing to the lability of the active principle in solution."

Experiments performed by Fleming, and others performed by Clutterbuck, Lovell and Raistrick in 1932, disclosed that penicillin was difficult to manipulate chemically, and it was described as a " very labile substance ", a view confirmed by Reid in 1935. Fleming clearly recognised that he

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had under investigation an antiseptic with unusually good properties, but the crucial point which has made penicillin so important in medicine, namely, the demonstration that it had chemotherapeutic powers of which practical use could be made, was only to be arrived at later—following a comprehensive investigation begun at Oxford ten years after the original announcement of the discovery of penicillin and when any idea that the substance might be of use in medicine had, apparently, been discarded, It should be remembered that the idea of antibacterial chemotherapy was much less familiar in 1929 than it became later, as a result of the introduction of the sulphonamides.

Start of the Work at Oxford: Early Laboratory Experiments

Statements have appeared from time to time that the work on penicillin at Oxford was started as an attempt to contribute to the treatment of septic wounds in the second world war. These give a false impression, however, as the work, of which wound treatment later became a part was initiated well before the outbreak of hostilities. Following discussions which had lasted many months, a plan was produced during 1939 by Dr. E. Chain and Professor (now Sir) Howard Florey for a comprehensive investigation from both the chemical and biological standpoints of some of the many antibiotics known at that time. The three chosen for the first studies were the products of *Ps. pyocyanea, Penicillium notatum,* and *B. subtilis*. Despite their conclusion, mentioned above, that penicillin was an extremely labile substance, Fleming and also Clutterbuck, Lovell and Raistrick had already shown in 1932 that under certain conditions a considerable degree of stability could be obtained with it. In view of this finding, it was felt by the Oxford workers, that there was a good chance of purifying the substance, at least to some extent, provided the right conditions could be found. The investigations on penicillin soon came to be so interesting that work at Oxford on other antibiotics gradually ceased, though the investigation of *Ps. pyocyanea* was continued for some time by Dr. R. Schoental. After some preliminary experiments had been made, a team of workers was gradually assembled for the various phases of the penicillin research; they were:—

Professor Florey, Dr. Chain, Professor A. D. Gardner, Dr. N. G. Heatley, Dr. E. P. Abraham, Dr. M. A. Jennings, Dr. J. Orr-Ewing, Dr. A. G. Sanders, and later, for the clinical work, Dr. C. M. Fletcher and Dr. M. E. (now Lady) Florey.

In addition to the Council, the Rockefeller Foundation of New York and the Nuffield Trust contributed to the cost of this programme.

First the mould was grown on the medium proposed by Raistrick and his colleagues, and the production of antibacterial activity was confirmed. Next a simple biological test was devised, by means of which the results of extraction and other chemical procedures could be followed. This test, now known as the cylinder plate method of assay, has proved of great practical value at all stages. The succeeding steps which led to the preparation of a stable dry powder were:—

(1) extraction of the penicillin into ether from the acidified crude broth, by the method which had been described by Clutterbuck *et al.* in 1932, (2) extraction of the penicillin from the ether into dilute alkali or buffer solution at about *p*H 7, and (3) lyophile drying of the neutral aqueous solution. Subsequently, other solvents were used instead of ether, and it is interesting to note that present manufacturing processes all involve,

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at some stage, a solvent transfer depending on the fact that the free acid is much more soluble in some organic solvents than in water, but that the reverse holds true for the salts of penicillin.

With the preparation of concentrates free from protein and inorganic salts, the way was open for all the subsequent observations. The chemical properties were investigated, the principal reasons for the lability of penicillin were established, and stable salts were prepared. The antibacterial capacity of the successive extracts was examined. *Staphylococcus aureus* and *Strep. haemolyticus* were inhibited by 1 part in 1,000,000 of one of the first dry preparations, while the gonococcus was even more sensitive to its action. Many other organisms were also sensitive to high dilutions, but *Bact. coli* and other gram-negative bacilli were found to be in various degrees resistant. Besides obtaining quantitive information on the relative sensitivity of different bacteria, the workers at Oxford were able to make some important additions to the list of sensitive and resistant organisms which Fleming had tested with his broth filtrate. In particular, it was shown that the clostridia of gas gangrene and a strain of *Actinomyces bovis* were sensitive to penicillin, and that the tubercle bacillus was not. Variations in sensitivity between different strains of the same organism were also noted, as Fleming had found with *Strep. viridans*. While these antibacterial properties were of interest, the substance would have been of little practical value unless this characteristic had been retained in the presence of the constituents of normal and inflamed tissues. All the sulphonamides known at that time were largely or completely inactivated by the constituents of pus and other breakdown products of the tissues, and were active in the presence of a relatively small number of organisms only. It was shown that penicillin—a product of entirely different nature—retained its full activity in the presence of pus, blood serum, and tissue autolysates, and that variations in the size of the inoculum of bacteria had a comparatively small influence on its inhibitory powers.

Protective Experiments in Animals

It was in May, 1940, that the first attempts were made to find whether an extract of the *Penicillium* exerted any protective effect on mice infected with streptococci. As the active material was at that time both scanty and precious, these experiments were of limited scope; nevertheless, the results were encouraging, and experience was gained as to the size and frequency of dose, and the duration of treatment, necessary to produce an optimal effect. Based on this information, a larger series of tests was carried out at the end of June and the beginning of July, 1940, and these showed conclusively that penicillin injected subcutaneously could protect an animal from an infection induced by staphylococci or streptococci injected intraperitoneally, which would ordinarily have been fatal; the animals showed no toxic symptoms from the injections. The same method of treatment was effective against lethal doses of spores of *Cl. septicum* injected intramuscularly. These results were published in the *Lancet*, 1940, **ii**, 226.

Thus a new property of penicillin was disclosed. It was shewn to be a true systemic chemotherapeutic agent—that is to say, when absorbed into the blood stream after administration, it would arrest a distant or a generalised infection without itself doing harm to the animal. It will be understood that the investigations here described in sequence were in many instances proceeding concurrently. Among experiments which were done early were those concerned with the behaviour of the *Penicillium* extract

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towards living tissues *in vitro* and *in situ*. Whereas staphylococci were inhibited by early crude preparations at about 1 part in 1,000,000, human leucocytes *in vitro* remained active in a 1 in 1,000 solution for at least three hours. Later it was shewn by Medawar and by Jacoby that there was the same large gap between the concentration which produced bacterial inhibition and that which interfered with the growth of tissues in culture. Intravenous injections of as much as 10 mg. of the impure substance (containing perhaps about 400 units) in 0.3 c.c. of distilled water were tolerated without disturbance by mice weighing 20 g. and, later, purer preparations were shewn to be even less toxic (Florey and Jennings, 1942). Other pharmacological investigations were made in animals, all of which reinforced the view that the extracts were remarkably free from poisonous effects. It was also established that penicillin was absorbed from the subcutaneous tissues, muscles and small intestine, and was rapidly excreted and concentrated in the urine. It was later shown that penicillin appeared in the bile of animals, though not in substantial amounts in their cerebrospinal fluid, tears or pancreatic juice.

From these and from the concurrent chemical investigations, a good knowledge was obtained of the behaviour of penicillin in the body, so that, even before the first patient was treated, the lines along which therapy would have to be planned had been formulated. For instance, the rapid excretion of penicillin in the urine made frequent or continuous injections imperative if an effective level of the drug was to be maintained in the blood; its destruction by acid was a contraindication to giving it by the mouth, and the finding that it could be destroyed by certain bacteria showed the need to keep penicillin solutions sterile. A full account of these investigations, together with a description of the first clinical trials, was published in the *Lancet*, 1941, **ii**, 177.

The "Oxford Unit" of Penicillin Activity: Relation to Subsequent International Unit

Early in the work, it became clear that to express the potency of the various extracts, a system of units would be much more convenient than the use of such terms as "15 milligrams of material inhibiting *Staph. aureus* at 1 in 640,000 but not at 1,280,000," etc. A particular buffer solution of partially purified penicillin was therefore taken as a standard, and the unit was defined as the amount of penicillin contained in 1 ml. of this solution. This unit, transferred, of course, to other standard preparations, was used at Oxford, and was afterwards almost universally adopted by workers elsewhere under the designation of the "Oxford Unit." Later, the International Penicillin Unit, proposed by a committee of the League of Nations Health Organisation in October, 1944, was fixed at approximately the same value (p. 244).

Early Efforts to Increase Production

Because penicillin was formed only in minute amounts in the metabolism fluid of the fungus, production in the laboratory, by the improvised methods at first available, was very slow, and it seemed that the only way to procure enough material for further progress at a reasonable speed was to seek the aid of a commercial firm. The first approach of this nature was made from Oxford in July, 1940, but soon afterwards one of the worst periods of bombing began, and, because of this and other difficulties in industrial production, it was decided to endeavour to brew and extract at Oxford sufficient material for trials on disease in man. It was realised that unless clinical results could be obtained which were as striking as those recorded in the animal experiments,

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it was highly improbable that any firm would embark on really large-scale production of penicillin. The difficulties in raising the scale of laboratory production were formidable; it was necessary to decide whether it would be more profitable to try to accumulate material from the small yield per litre which was then obtainable, until enough had been made for trial in man, or whether to hold up production while a search was made into the possible means of increasing the yield. The former policy was adopted—probably rightly, as it was only after the first demonstration of chemotherapeutic effectiveness in man that it was possible to justify large-scale investigations by industrial and other research bodies. However, simultaneously with the introduction of laboratory brewing of penicillin on a major scale at Oxford, attempts were made to increase the yield by changes in composition of the medium and by selection of strains. These investigations gave no useful results at the time, though more extended studies on similar lines gave most valuable results later in America.

For the laboratory large-scale production, there was a need for vessels more economical of incubator and steriliser space, and more convenient to handle, than the Erlenmeyer flasks initially used. Rectangular vessels with a side-arm were designed, and were specially constructed of porcelain (glass being at that time unobtainable). These vessels were designed to hold 1 litre of fluid in a layer about 1.7 cm. deep.

The raising of the scale of brewing immediately brought with it problems connected with extraction. Separating funnels were no longer adequate, and none of the laboratory counter-current extractors which had been described at that time was suitable, owing to the *p*H lability of penicillin and the formation of emulsion. After some unsuccessful attempts, a workable counter-current extraction apparatus was constructed, and this was used for more than a year, until it was superseded. Difficulties of biological origin had also to be overcome. More than once the mould ceased to produce the active substances, and this was countered by paying particular attention to the inoculating cultures. A series of single spore isolations having been tested for yield of penicillin, a large number of subcultures of the most productive strain was made. As soon as these were well spored, they were stored in a refrigerator until required; from these, subcultures for sowing the vessels were obtained; later, master cultures of proved strains were preserved by lyophil drying. Then again, not infrequently the metabolism fluid was found to have lost its penicillin activity, because of contamination by air organisms; some of these produce an enzyme (penicillinase) which destroys penicillin, and the consequent necessity for absolute sterility during the growth of the mould added enormously to the manufacturing difficulties. The months spent in increasing the output, with all their disappointments and difficulties, are not likely to be forgotten by those involved. Undoubtedly the possibility that the drug might be of value in treating war injuries provided by this time a powerful stimulus to persevere.

The word "penicillin" has been used in several senses. Originally, it referred to the broth on which the mould was grown; then it referred to the active substance in the broth; now it is applied to the material available for clinical use, and also to the pure substance. It is now known that the first dried extracts used at Oxford contained not more than 1 to 2 per cent. of the active substance, and the first material for clinical use contained about 5 per cent.; material containing 10 per cent. was considered unusually pure. This contrasts with the eventual use of virtually pure penicillin for clinical purposes. Although these relatively crude preparations had some minor disadvantages, they gave generally satisfactory clinical results, and it was indeed most fortunate that the impurities accompanying penicillin were so little toxic.

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The product of the laboratory large-scale work was required for two purposes —for chemical investigations and for trial in disease in man. All the early work was dominated by the struggle to accumulate even a few hundred milligrammes of the impure material for these purposes. Those who now use penicillin freely whenever they wish, may find it difficult to believe that only a few years ago the drug was so precious that even the traces remaining in test tubes and syringes were washed out and saved.

Early Clinical Trials at Oxford

By the beginning of 1941, enough material and evidence had been collected to warrant a few trial injections in man. On 27th January, 1941, the first patient to receive a parenteral injection of penicillin was given intravenously 100 mg. of material, 10 mg. of which had had no ill effect on a 20 g. mouse. The patient, who was in the Radcliffe Infirmary, Oxford, was not suffering from any bacterial infection, but had an inoperable carcinoma. There was no reaction immediately after the injection, but three hours later there was a sharp rise of temperature with a rigor. Another injection, into a different patient, showed without doubt that the material was pyrogenic (i.e. capable of producing fever), a fact which was confirmed in rabbits. Fortunately, the pyrogenic agent proved not to be the same as the therapeutically active component, and it was possible by the use of chromatography to separate the two. When this difficulty had been overcome, enough material was collected to use on the first case of infection in man, routine pyrogen testing in rabbits being adopted for all material used for clinical purposes.

It was natural that the first cases made available for treatment should nearly all have been of the most severe type, in which all other possible treatments had failed. Though this selection was not governed by scientific considerations and entailed a severe test for the new drug, it had the advantage that the results were highly significant and easy to interpret. Five of the first six patients had serious staphylococcal or streptococcal infections which had not been controlled by surgical measures and sulphonamide therapy. The first, the treatment of whom was begun at the Radcliffe Infirmary on 12th February, 1941, had a severe staphylococcal infection with abscess formation and osteomyelitis. There was little idea at that time of how long treatment might need to be continued, and after five days, when considerable clinical improvement had been noted, the meagre stock of penicillin was exhausted; eventually the patient relapsed and died. The next patient, who was treated at the Wingfield-Morris Orthopaedic Hospital, was a boy with acute osteomyelitis due to a haemolytic streptococcus, which had not responded to other treatment. Following the intravenous administration of penicillin for five days the infection appeared to be completely controlled, but about four weeks later the patient relapsed. These first two cases are typical of those which receive too little treatment. The struggle to make more penicillin was continued, and the later patients of the series were treated with greater success; the results confirmed the potentialities which the laboratory work had revealed. Several of the patients were children, who were chosen partly with the idea that less penicillin might be needed to treat them than to treat adults. A report on this series of cases, together with a detailed account of the methods of preparation, the pharmacological and the bacteriological properties of penicillin, was published in the *Lancet*, 1941, **ii**, 177.

These early trials confirmed the opinion already reached that substantial doses of penicillin were not harmful to man—in fact, on the contrary, one of the striking features was the improved appetite and feeling of well-being of very seriously ill patients within two or three days from the beginning of treatment—and they gave a very good indication that the most severe

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infections by pyogenic bacteria could be controlled. The effect on staphylococcal infections was especially important, as the sulphonamides then known were of little value in these conditions. The results in some of the patients were so favourable that the work demanded further expansion, whatever the difficulties. Just how formidable an undertaking the preparation of penicillin was at that time, can be illustrated by the fact that one case of severe sepsis might need the brewing and processing of as much as 2,000 litres of medium.

Further Efforts to increase Production: Work in U.S.A. and U.K.

It has already been indicated that, because of the war situation in Great Britain in 1941, the prospect of early commercial manufacture of any substantial amount of penicillin here was slight. Dr. Weaver, of the Natural Sciences Division of the Rockefeller Foundation, was accordingly approached with the suggestion that an attempt should be made in the U.S.A. to prepare larger quantities of penicillin for further clinical trials. As a result of this, Professor Florey and Dr. Heatley went to the United States in June of that year. They had discussions at the Northern Regional Research Laboratory, Peoria, of the U.S. Department of Agriculture, which were afterwards fruitful in the field of industrial production, and several American manufacturing firms were visited. Dr. Heatley worked first at Peoria and then with Merck & Co., Inc., imparting all the available information, with a view to promoting the most rapid development of large-scale production. A high tribute must be paid to the enterprise and energy with which the American manufacturing firms undertook production of the drug. Had it not been for their efforts, there certainly would not have been sufficient penicillin by " D-day " in 1944, to treat all severe casualties, both British and American, in the final campaign in Europe.

The fact that very little penicillin was available from either British or American manufacturing sources in 1941-42 spurred the Oxford workers to further efforts; brewing was increased, and a larger extraction apparatus of a different type was constructed. This depended on emulsifying acidified brew with amyl acetate, and breaking the emulsion with a Sharples centrifuge. Help was in time received from Kemball, Bishop & Co., Ltd., who, in September, 1942, began to brew material in London and to bring the crude medium in 150 and 200 gallon lots (in milk churns) to Oxford, where it was put through the extraction plant. By the middle of 1942, small-scale commercial production by surface culture methods was also being carried out by Imperial Chemical (Pharmaceuticals), Ltd., who supplied material for some of the clinical investigations.

Later Clinical Trials at Oxford and elsewhere in Britain

As soon as enough penicillin had been accumulated, a further series of clinical trials was started. These were carried out in the Radcliffe Infirmary, the Wingfield-Morris Hospital, the 101st General Hospital (Army) and the R.A.F. Hospital at Halton. An arbitrary dose of 1,000 units per lb. of body weight per 24 hours was found to be effective in several cases, but it was soon realised that a method for estimating the amount of the drug in the blood would be needed in order to control the size of the dose and to ensure effective treatment. The cylinder-plate method, which was tried at first, was not sufficiently sensitive, so a simple slide dilution method, requiring only a drop of blood, was devised. The principle was always maintained that a concentration of penicillin which would demonstrably inhibit the infecting organism should be present in the blood as nearly continuously as possible. With the aid of the slide dilution test it was possible to formulate

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a basic dose and frequency of administration, which experience has shown to be adequate for the treatment of the majority of sensitive infections. The figure arrived at, 15,000 units 3-hourly for an adult, was afterwards confirmed both here and, independently, by workers in the U.S.A.

The account of this series of cases, which comprised 15 treated by general and 172 by local administration, was published in the *Lancet*, 1943, **i**, 387. Of the 15 patients with serious illnesses, 13 were treated with penicillin by intravenous or intramuscular injection, and all ten with severe staphylococcal infections recovered, as did also a patient with streptococcal meningitis. A patient with subacute bacterial endocarditis improved during treatment, but relapsed when the penicillin was stopped (see also p. 90). Two patients with actinomycosis, to whom the dosage given was probably inadequate, yielded no definite information; and in one patient a streptothrix infection appeared to be eliminated. In the majority of the 172 patients with miscellaneous septic conditions treated by the local application of penicillin, staphylococci and streptococci were eliminated from the lesions and healing occurred.

With the co-operation of Mr. R. G. Macbeth and Mr. G. H. Livingstone, a group of patients operated on for suppurative mastoiditis was treated by local instillation of penicillin through tubes, after complete suture of the wound. This method was later adopted with success in North Africa to treat war wounds. The adaptation of the usual methods of local treatment to the requirements of penicillin therapy was among the most interesting technical parts of the clinical work, the object always being to keep the penicillin in contact continuously with all infected parts. Thus, a chronic sinus, after penicillin had been inserted, was occluded with a rubber bung, and drainage tubes, even in septic wounds, were opened only at intervals to aspirate exudate and insert more penicillin. The same principle has had extensions in other fields of surgery.

Penicillin Treatment of War Wounds and Burns

Simultaneously with the work just described, the first attempts were made to control sepsis in burns with penicillin. Dr. Leonard Colebrook and his collaborators, in the Council's Burns Unit at the Royal Infirmary, Glasgow (p. 270), and Wing Commander D. C. Bodenham at the R.A.F. Hospital, Halton, were able to control streptococcal and, to a less extent, staphylococcal infections by local applications of penicillin supplied from Oxford. Bodenham was the first to dilute penicillin with sulphanilamide powder for local application.

The first use of penicillin in war wounds was initiated in April 1942, when a small quantity of penicillin, prepared in Oxford, was offered to Major-General L. T. Poole, Director of Pathology, War Office, and was despatched to the Middle East. This material, which contained 30 to 40 units per milligramme, was used by Lieut.-Colonel R. J. V. Pulvertaft for local application to wounds which had long been suppurating. The results, which could be described as encouraging in spite of the difficult character of the cases, were reported in 1942 and published in 1943.

The main attack on the treatment of war wounds with penicillin began early in 1943, when sufficient quantities were available from the laboratory at Oxford, Messrs. Kemball, Bishop & Co., Ltd., and Imperial Chemical Industries (Pharmaceuticals), Ltd., to make it worth while for the Army to send special investigators to North Africa. For this purpose, Lieut.-Colonel Ian Fraser, R.A.M.C., a surgeon, and Major Scott Thomson, R.A.M.C.,

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a bacteriologist, after preliminary training in penicillin techniques at Oxford, went to Algiers in May, 1943. About three weeks later Professor Florey and, a month after that, Brigadier H. Cairns also went to North Africa, bringing further supplies of penicillin from the Therapeutic Research Corporation. In a confidential report presented to the War Office and the Medical Research Council in October, 1943, it was stated:—

"It should be clearly understood that the object was not primarily to ascertain whether penicillin was capable of dealing with gram-positive organisms in septic conditions; this we consider has been amply shown in England already. The main problem was to learn to employ the small quantities of penicillin likely to be available for service use to the best advantage. The work, then, has been designed to give an answer to the questions: can penicillin be used effectively in the field at all; and, if so, how much is required, and at what place in the Army organisation can it be used to the best advantage?"

The first patients treated in this study all had chronic sepsis, of duration varying from a few weeks to many months. Though some preliminary trials showed that superficial sepsis could be greatly benefited by local applications of penicillin and that parenteral administration offered hopes for the successful treatment of deep-seated infections, owing to the extremely limited supplies of penicillin then available very few patients could be given it parenterally. As a result of this work, it was realised that "it was far too late to start penicillin treatment weeks or months after wounding, at a Rear Base hospital, and that its use should be tried much earlier, before the establishment of serious infection."

Accordingly, a new scheme was devised for treating the expected casualties from the impending invasion of Sicily. It was arranged to receive them, as soon as possible after wounding, in Base Hospitals at Sousse and Tripoli, where penicillin therapy could be started with the minimum of delay. To implement this plan, the help of a number of experienced war surgeons and pathologists was obtained; they included, among others, Lieut.-Colonels J. S. Jeffrey, R.A.M.C., A. L. d'Abreu, R.A.M.C., E. L. Button, N.Z.A.M.C., and D. W. Jolly, R.A.M.C., together with Majors K. C. Eden, R.A.M.C., H. L. deWaal, R.A.M.C., and W. E. Hamilton, R.A.M.C. The decision was made to close wounds by suture at the first definitive operation performed at the Base Hospital, relying on the local, and sometimes also parenteral, use of penicillin to suppress or abolish sepsis at that stage and to permit early healing.

Casualties were received at the Forward Base from two to 22 days after wounding: a few of the airborne and area troops had wounds of less than 12 hours' duration. Their previous treatment usually included surgical excision, together with sulphonamide therapy (local and systemic). Nearly all the men, on arrival at the Forward Base, had wounds so infected that the surgeons concerned in this trial would not ordinarily have considered closure without further preparatory treatment.

The result of the decision to combine immediate suture with penicillin therapy was that, of 171 soft tissue wounds, some of the most severe type, 104 healed completely, while in only 7 did the suture line entirely break down.

The results in severe compound fractures of the femur, treated parenterally with penicillin after suture, were less good, though those in compound fractures of other bones were encouraging. Some preliminary trials in the treatment of head wounds were also made at this time.

Further developments of the work were possible in the Italian campaign, for which Lieut.-Colonel Jeffrey was appointed Penicillin Officer and Major

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Scott Thomson, Bacteriologist. Large numbers of cases were treated on the lines already formulated, and with increasing experience—and the widespread adoption of the "two-stage" operation (p. 35)—great improvements in the end-results both of soft tissue wounds and of fractures were recorded. Moreover, penicillin therapy was used with good effect in the treatment of wounds of special types, such as those of the head and thorax.

By 1944, when the invasion of Normandy was about to begin, the situation was entirely different from when the first trials were carried out on war casualties, in that there was ample penicillin for all who needed it. As the result of the greatly improved supplies, the Army Medical Service was able to organise, on the widest possible scale, prophylactic treatment against sepsis, by parenteral injections beginning within 24 hours of wounding.

It is thus possible to trace directly, as far as British practice is concerned, firstly the establishment in the laboratory of all the necessary data for the preparation and administration of penicillin and then, based on those data, the employment of the drug in the clinic in the treatment of septic conditions both by parenteral injection and by local application. Much of the success attending the use of penicillin for the treatment of the wounded is to be attributed to the high quality of war surgery, and this again received a great stimulus because surgeons provided with penicillin were able to suture even the most severe wounds without the danger of major sepsis. Further reference to the place of penicillin in the treatment of the wounded is made on pp. 18-19 and 32-37.

The Origin and Work of the Penicillin Clinical Trials Committee

The Penicillin Clinical Trials Committee (p. 418) was appointed by the Council in March, 1943, under the chairmanship of Professor H. R. Dean. The situation leading to its formation was, briefly, as follows. The work at Oxford which has been described above had made it clear that penicillin was a chemotherapeutic agent of great importance, but while many of the potentialities of the new drug had been demonstrated, its promise in other directions remained to be explored. Such a task was beyond the capacity of any one institution or group of workers, and it was considered desirable to widen the field of clinical study. Although the commercial production of penicillin at last promised a substantial yield, supplies of the drug were still very limited at this time; it was therefore necessary to arrange for the control of penicillin distribution by a responsible body, which would ensure that the available stocks were used to the best advantage. The Committee's function was to increase knowledge of penicillin therapy by developing improved technical methods of administration, and by extending the range of use of the drug to include conditions in which experience of its action was lacking; of the latter conditions, many were caused by bacteria known to be susceptible *in vitro* to the action of penicillin.

This was a difficult objective to reconcile with humanitarian claims, and for many months, owing to the extreme scarcity of penicillin, the Committee, and those who tested the drug on the Committee's behalf, were compelled to refuse treatment which might have proved beneficial to individual patients but would not advance knowledge of the drug's action. So grave was the shortage at that time, that there would not have been nearly enough penicillin to treat only the cases of staphylococcal septicaemia which came to the Committee's notice; and, of all diseases, this most imperatively demands penicillin treatment. Both then, and later when the availability of increased supplies warranted a certain amount of routine treatment as well as research, the relative

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merits of its different uses—life-saving in septicaemia, reduction in the period of incapacity of key fighting personnel with less serious infections, and the prevention of disablement following accidents to war-factory workers—repeatedly involved the gravest questions of principle and the most difficult decisions. The last such decision was taken as late as January, 1945, when, despite the heavy expenditure of penicillin involved, it was determined to embark on the treatment of cases of subacute bacterial endocarditis.

In the early stages of the clinical trial of penicillin, there was complete agreement on one point: that the first priority should be given to the treatment of patients with war wounds.

The amount of penicillin initially available sufficed only to supply each of four centres with about 6,000,000 units of penicillin monthly. The centres were situated at the Radcliffe Infirmary, Oxford, and at St. Mary's, the Middlesex, and St. Bartholomew's Hospitals, London. A further supply was allocated to the School of Pathology at Oxford for the continuation of research into the chemical constitution of penicillin (see pp. 90-95).

As the existence and purpose of the Committee became known, a great flow of requests for grants of penicillin for various purposes began. Although large numbers of these had to be refused, it was possible to accede to many which were accompanied by proposals for original and promising lines of study. Fortunately, the amounts required were often small, and supplies steadily, though slowly, increased. Eventually, grants of penicillin were being made to forty-two centres for specific lines of research—general medicine and surgery (8 centres), orthopaedics (5 centres), neurosurgery (5 centres), burns (9 centres), ophthalmic conditions (4 centres), chest injuries and diseases (3 centres), ear, nose and throat conditions (3 centres), puerperal septicaemia (1 centre), diseases of children (2 centres), venereal disease (2 centres), and more recently bacterial endocarditis (14 centres). Some of these centres received as little penicillin as 100,000 units a month, and the total of 100 million units a month, which was distributed, represented but a fraction of what was at that time being used in America. The emphasis which had to be laid on economy was not wholly disadvantageous, however, since it encouraged attempts to use penicillin by the less extravagant method of direct local application rather than by systemic injection, and this unexplored field proved highly fruitful. In the treatment of battle casualties the British Army continued to use penicillin by local application in many types of wounds, long after lease-lend penicillin had become plentiful; and the local application of penicillin in the treatment of diseases of the skin, in burns, in mouth infections, in infections of the serous cavities and meninges, and in various other conditions, was largely developed in the Council's research centres. Progress in investigating the systemic use of penicillin was at first hampered by lack of supplies, but much information of practical value was gained at this time. Reports from the various research centres were submitted at regular intervals, and the Committee arranged for their dissemination both in this country and abroad. Most of these reports have since been published in medical journals.

Almost the whole of the work on which the present knowledge of penicillin therapy is based was done in Great Britain and the United States. Although penicillin was a British discovery, U.S. workers had the advantage of enormously greater supplies of the drug in its early years; study at many centres in America had begun months before anyone outside Oxford had handled penicillin in England, and American output reached a spectacular level while ours was little more than a scanty trickle. Only when American penicillin was placed at the free disposal of our fighting services was it possible for British clinicians to use it on an adequate scale. Nevertheless, it was in

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the early days of scarcity that the most substantial contributions to knowledge were made by British investigators, and these, almost without exception, were working on behalf of the Council.

An important part of this work was the treatment of a sufficient number of cases of infections known to respond to penicillin in order to define appropriate dosage, to improve methods of administration and laboratory control, and to observe the effect of various factors on prognosis; in this way, it was possible to formulate optimum therapeutic policy. This was the main task of the four original centres, each of which also developed its own particular interests. At St. Mary's Hospital, London, Professor Sir Alexander Fleming and his colleagues made a thorough study of the effect of single and multiple doses, by various routes, on the penicillin content of the blood, and of methods for determining the penicillin content of body fluids; this centre also undertook the treatment of gonorrhoea and its complications. At the Middlesex Hospital, pioneer work was done on the treatment of pneumonia; while at St. Bartholomew's Hospital the method of giving penicillin by intramuscular drip was explored, as was the use of penicillin locally in the treatment of skin diseases.

Several individual studies, also, call for special mention. A very important one was that initiated in North Africa in 1943 by Professor Florey and Brigadier Cairns, on methods of treating war wounds (pp. 35 and 86). A large proportion of the supplies of penicillin then available was devoted to this.

Another important study was that of Brigadier Cairns and his colleagues on the penicillin treatment of septic meningitis; the best ways of using the drug in these dangerous cases were carefully tested at the Hospital for Head Injuries, Oxford. Clinicians receiving supplies of penicillin from the Committee also contributed largely to defining the necessary conditions for success in the treatment of osteomyelitis, and to determining the best methods of applying penicillin in the treatment of infections of the pleura and lung. The first centre for the penicillin treatment of syphilis in England was established at Liverpool. The treatment of infections of the mouth and throat by means of penicillin pastilles was developed at one of the centres established by the Council.

As well as acting in an advisory capacity to the Ministry of Supply and the Ministry of Health on numerous problems relating to the production and distribution of penicillin, the Committee undertook to arrange the training of surgeons and pathologists in this country in the proper uses of the drug; it also had a major share in planning the arrangements for penicillin treatment of air-raid casualties and of the large number of battle casualties expected after " D-day " (see p. 31). The first step to these ends was the issue by the Council of *War Memorandum* No. 12 on " The Use of Penicillin in Treating War Wounds ", which was prepared by the Committee. On the basis of this memorandum and of subsequent work, courses in the clinical uses and laboratory control of penicillin therapy were provided at the three principal penicillin research centres in London. Surgeons and pathologists were selected by the Ministry of Health from the various regions in England, so that they in turn could pass on the information to those likely to be concerned with the treatment of war casualties. Between February and May, 1944, 260 surgeons and pathologists received this course of instruction at the centres established at St. Mary's, the Middlesex and St. Bartholomew's Hospitals.

At the same time a small sub-committee undertook to advise the Emergency Medical Services on the equipment and organisation which would be required for the penicillin treatment of battle casualties. This was no simple matter, since severely injured casualties had to receive three-hourly injections of the

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drug in ambulance trains, transit hospitals, and at ports, as well as in base hospitals. This organisation, which was set up at short notice, worked efficiently, and most casualties who could benefit from penicillin received a regular series of injections starting at the Field Transfusion Unit and continuing throughout transit to the Base Hospital. Centres to investigate special problems bearing on the treatment of battle casualties with penicillin were formed in three of the Transit Hospitals and in an Air Port Hospital, and arrangements were made for the results of penicillin treatment in wounds of different types to be analysed statistically (p. 36).

The most recent activity of the Penicillin Clinical Trials Committee has been to investigate the treatment of subacute bacterial endocarditis: this is being done on a scale large enough to provide information as to the system of dosage best suited to the disease. Fourteen centres in England, Wales, Scotland and Ireland have taken part in a co-ordinated study, and between February, 1945, and February, 1946, 201 cases were treated. A preliminary report on this investigation, published in 1946, shows clearly that while the scale of penicillin dosage appropriate to diseases other than subacute bacterial endocarditis is usually ineffective in that condition, the administration of larger doses for 28 days or more can almost always cure it in its early stages. Before the introduction of penicillin therapy there had been hardly any recorded instances of recovery from subacute bacterial endocarditis, but this disease now takes its place in the list of severe and often lethal infections for the victims of which early and adequate treatment with penicillin offers new hope.

The Chemistry of Penicillin

As soon as the early laboratory experiments mentioned on pp. 79-81 had shown that penicillin had chemotherapeutic properties, work was begun by Dr. E. P. Abraham and Dr. E. Chain on the further purification of the crude extracts then available. The final aims of this work were to elucidate the structure of penicillin and, if possible, to produce it synthetically.

All that was known at that time (1940) about the chemical nature of penicillin was that it was a labile acid of relatively low molecular weight. One of the first studies made at Oxford dealt with the conditions under which penicillin was inactivated, since a knowledge of these was essential if suitable methods were to be developed for its purification. It was found that although penicillin was quickly destroyed at ordinary temperatures in acid or alkaline solution, it was stable enough, when cooled, to permit extraction with ether or amyl acetate, in the form of its free acid. Treatment with a number of oxidising agents led to rapid inactivation, but catalytic hydrogenation or reduction with aluminium amalgam caused no loss of activity. Various metallic ions, such as those of copper and mercury, free primary and secondary bases, and primary alcohols, and an enzyme, penicillinase, found to be present in certain bacteria, were all shown to destroy the active substance.

In view of the instability of penicillin, attention was concentrated on methods of purification depending on the partition of the active substance between organic solvents and water at various reactions, and on adsorption. Distribution procedures, combined with chromatographic adsorption on columns of alumina from ethereal solutions, led in 1941 to the preparation of material with an activity of 150 units per mg. This activity was doubled by treating the preparation with aluminium amalgam, when impurities were adsorbed on the alumina formed in the reaction, and further chromatography subsequently raised the activity to a value then estimated at 500 units per mg. On the discovery of an error in the standard used during that period at Oxford, it appeared that the actual activity of this partly purified preparation was

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probably nearer to 700 units per mg. It was found that when the material was inactivated with dilute acid a new titratable group appeared, and that a different titratable group was liberated by dilute alkali, while carbon dioxide was evolved on hydrolysis with hot acid or alkali.

This preparation of penicillin inhibited the growth of staphylococci at a dilution of 1 in more than 24 million. Its high activity, its apparent homogeneity on an alumina column, and the fact that its inactivation was accompanied by well defined physico-chemical changes, prompted the hope that it was indeed nearly pure. Attempts were therefore made to isolate degradation products from it, as well as to increase its degree of purity. Although it was later shown to contain not more than 50 per cent. of penicillin, the decision to investigate it chemically proved to be sound.

At this time (1941-42), Sir Robert Robinson and Dr. (now Professor) W. Baker, of the Dyson Perrins Laboratory, Oxford, joined with Dr. Abraham and Dr. Chain to form the nucleus of a team which continued the study of the chemistry of penicillin at Oxford, and to which Dr. J. W. Cornforth later became a valuable addition. Most of the penicillin used in this work was produced in the Sir William Dunn School of Pathology. A continual difficulty was the very small amount of material procurable for investigation; it was thus very fortunate that the team subsequently had the help of Dr. Dorothy Crowfoot and Dr. B. Low, in the Oxford Department of Crystallography, who supplied X-ray crystallographic data about minute quantities of crystalline degradation products, and of Dr. E. R. Holiday, from the London Hospital, working in the Department of Biochemistry, Oxford, who measured and interpreted ultra-violet absorption spectra.

The first crystalline degradation product of penicillin—the amino-acid penicillamine—was isolated at Oxford from material which had been hydrolysed with hot acid; an account of this work was published by Abraham, Baker, Chain and Robinson in 1943. Not long afterwards, Duffin and Smith, of the Wellcome Foundation, showed that a crystalline substance, which they named penillic acid, was formed when penicillin preparations were inactivated with dilute acid at room temperature.

As soon as it became apparent that the use of penicillin in war medicine might provide a valuable means of conserving man-power, it followed that the discovery of a workable synthesis of the drug would be a substantial contribution to the war effort of the Allies and of corresponding value to the enemy; an official ban on the publication of the results of further chemical work was therefore imposed early in 1943. From this time until the end of 1943, those studying penicillin chemistry in England sent dated and confidential reports to the chairman of an unofficial body known as the " Penicillin Chemical Committee ", which had originally been formed in November 1942 from representatives of both academic and commercial institutions for the purpose of pooling information in this field.

In May, 1943, it was reported from Oxford that when purified penicillin was inactivated in aqueous solution at *p*H2, a substance was formed which had two acidic groups and one basic group, but which, while very similar to penillic acid, was, according to X-ray crystallographic data, not identical with it. This substance was later found to be a crystalline modification of penillic acid, obtained from one form of penicillin when this is contaminated with small amounts of another. A new and stable compound, however, was found to be produced, together with carbon dioxide, when either acid-inactivated penicillin or penillic acid was treated with aqueous mercuric chloride. This compound contained one acidic and one basic group, and was called penillamine. On hydrolysis with acid at 100°C., penillic acid, like the purified penicillin, yielded carbon dioxide and a solution from which penicillamine could be precipitated by mercuric chloride.

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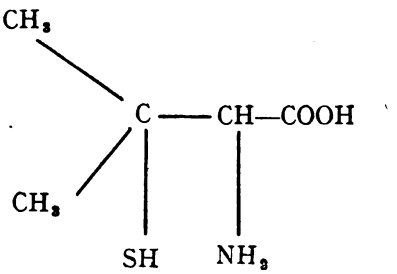
Up to this time it had been thought, owing to an unaccountable analytical error, that the best preparations of penicillin contained only carbon hydrogen, oxygen and nitrogen. The discovery that sulphur also was present, which was made at Oxford in July, 1943, enabled the correct formulae to be put forward (at Oxford and at the Wellcome Foundation) for penillic acid ($C_{14}H_{20}O_4N_2S$) and penillamine ($C_{13}H_{20}O_2N_2S$), and immediately led to the realisation that penillamine and penicillamine contained a free thiol group, while penicillin and penillic acid did not.

During this period further progress had been made with the problem of purification, and the finding that penillic acid could be isolated in 75 per cent. yield from the most active preparations of the barium salt of penicillin obtained at Oxford was reason for believing that these preparations were approaching a high degree of purity. In this work, the barium salt of penicillin had been used as a routine because, unlike the salts of the alkali metals, it is not hygroscopic. In August, 1943, however, the Council received information that a sodium salt of penicillin had been crystallised by Wintersteiner and MacPhillamy in the U.S.A., and it was then found that the sodium salt of the best Oxford material, although still contaminated with small amounts of impurities, crystallised spontaneously. This confirmed the conclusion already reached, that the process of purification was nearing its final stage, and the correct formula ($C_{14}H_{19}O_4N_2S^{Ba}/_2$) was put forward for the barium salt of the penicillin concerned.

By that time sufficient information was available about the properties of the American penicillin, produced in submerged culture, and the British penicillin, obtained by surface culture, to make it evident that these two products were not identical. The British substance was then referred to as Penicillin I (or F), and the American as Penicillin II (or G).

Considerable progress was made at Oxford with the fundamental chemistry of penicillin I during the next two months. The correct formula for penicillamine was established as $C_5H_{11}O_2NS$, and the fact that this substance formed a thiazolidine with acetone indicated that it was an α-amino-β-thiol compound. Its complete structure was shown by synthesis to be that of β-thiolvaline **(1)**:—

(1)



On treatment with bromine water, penicillamine was oxidised to the corresponding sulphonic acid (penicillaminic acid).

The identification of penicillamine and carbon dioxide as products of the acid hydrolysis of penicillin I, left eight of the latter's 14 carbon atoms to be accounted for. These eight carbon atoms were present in an aldehyde, which was originally detected in the solution obtained on hydrolysing penicillin or penillic acid with hot acid; afterwards, it was obtained in better yield, together with penicillamine and carbon dioxide, by inactivating penicillin with cold alkali and treating the product with aqueous mercuric chloride. This substance, called penillo-I-aldehyde, had the formula $C_8H_{13}O_2N$. Dihydropenillo-I-aldehyde ($C_8H_{15}O_2N$) was subsequently isolated from

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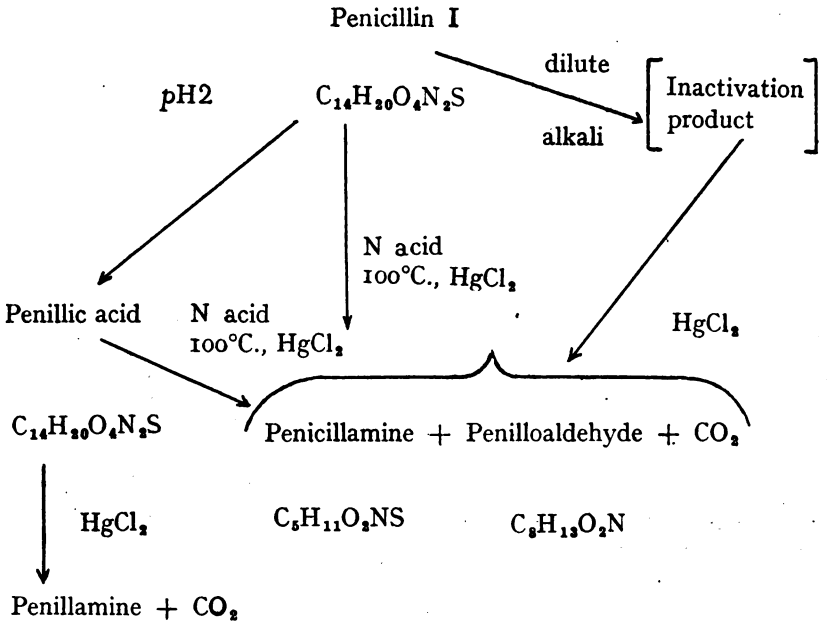
dihydropenicillin-I, which was obtained by the catalytic hydrogenation of penicillin I, by Cook and Heilbron and their colleagues at the Imperial College of Science, London. Further investigations at Oxford and at the Imperial College soon showed that penillo-I-aldehyde was β, γ-hexenoylaminoacetaldehyde (see (2) below) and that dihydropenillo-I-aldehyde was *n*-caproylaminoacetaldehyde. The correctness of these structures was confirmed at Oxford by synthesis.

(2) $CH_3CH_2CH = CHCH_2CONHCH_2CHO$

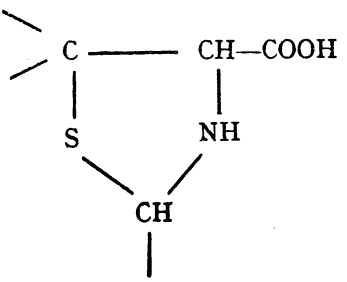
The results of the degradation work carried out on Penicillin I up to the end of 1943 can be summarised in the following scheme:—



$C_{13}H_{20}O_2N_2S$

Penicillin I itself was clearly derived from the condensation of penicillamine, penilloaldehyde and CO_2 with the elimination of two molecules of water. An immediate precursor of these degradation products was the substance, not then characterised, which resulted when penicillin was inactivated by alkali. A comparison of some of the properties of this substance with those of known thiazolidines had suggested that the former contained the structure (3):—

(3)



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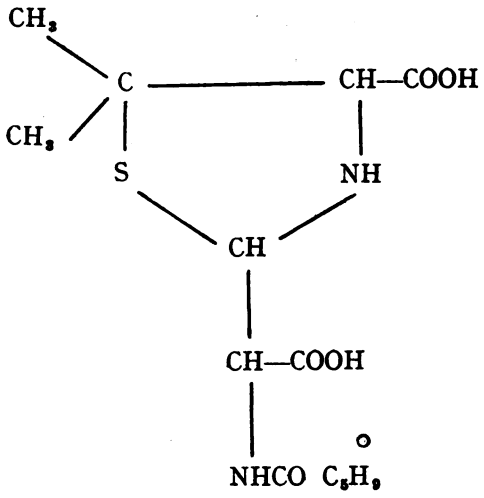
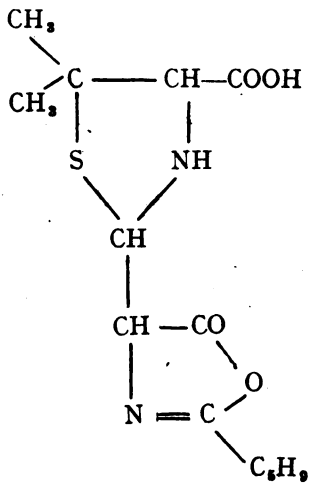
When the complete structures of penicillamine and penilloaldehyde were ascertained, (3) could be amplified to the structure (4), later known as penicilloic acid, the second carboxyl group being placed in the β-position to the potential aldehyde group to account for the ready loss of CO_2. Provided no re-arrangement of the penicillin molecule had occurred during its inactivation with alkali, the elimination of the elements of water in an appropriate manner from (4) would be expected to lead to the structure of penicillin itself.

(4)

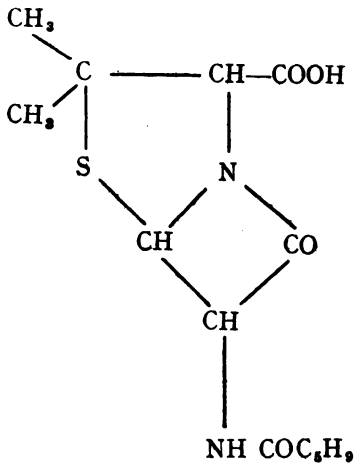


From the evidence then available, two formulae for penicillin I were put forward in a report by Abraham, Baker, Chain and Robinson, in October, 1943. One author suggested the " thiazolidine-oxazolone " formula (5) and the others the " β-lactam " formula (6):—

(5)



(6)



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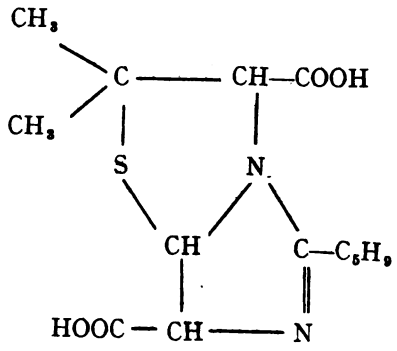
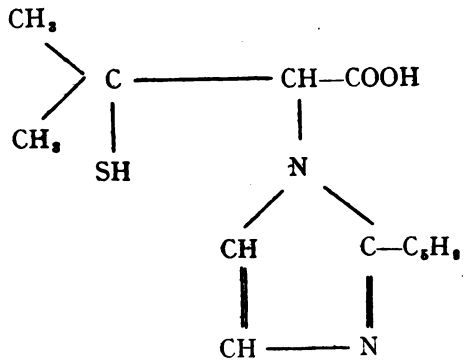
At the same time the correct structure (7) was assigned at Oxford to penillic-I-acid:—

(7)



The properties of penillamine-I made it difficult to imagine that this substance had any structure other than (8), which was given to it by the Imperial College team, and which was implied in the formula already suggested for penillic-I-acid:—

(8)



The close of 1943 saw the end of the first phase of the investigations on penicillin chemistry in England. By that time a growing volume of work was being carried out in the U.S.A. as well as in Britain, and liaison between workers in the two countries was established through a " Committee for Penicillin Synthesis ", under the chairmanship of Sir Robert Robinson, appointed by the Medical Research Council in London, and through the Committee on Medical Research of the Office of Scientific Research and Development in Washington.

Although structures other than (5) and (6) were subsequently suggested for penicillin, later Anglo-American work left only these two finally for consideration. The choice between them, however, proved curiously difficult, and it was not until 1945 that the β-lactam structure was shown conclusively to be correct.

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The feeding of the population of the United Kingdom, often under conditions of appalling difficulty due to the enemy sea and air blockade, was one of the outstanding achievements of the war. Despite the irksome restrictions of rationing, the fatigues and disappointments of "queueing", the inevitable limitation of the variety of foodstuffs to be purchased, and the reduced supply of fats and of animal protein, it is a fact that the diet of the nation as a whole was not only maintained at an adequate level in face of the enemy's fiercest efforts to starve us into surrender, but was planned more logically, distributed more equitably, and contained a higher proportion of certain health-producing food substances than ever before. Thus, while everyone was deprived of many dietary luxuries and variants, it is equally true that everyone had a fair share of the available foods, and that certain important nutrients were for the first time allocated on priority to those who needed them most, without regard to their economic circumstances. Research workers in nutrition had the satisfaction of seeing adopted, as measures of urgency under blockade conditions, a number of improvements in the national dietary for which they had pressed in vain for many years beforehand. Moreover, the time-lag between the gaining of knowledge by research and the practical application of such knowledge was materially reduced by the establishment of a much closer association between scientific experts and the Government. An instance of this was the case of calcifying factors in the diet, so important for the proper formation of the teeth and bones. It had long been stressed by nutrition workers that the pre-war diet of this country was notably deficient in calcifying properties, and the researches mentioned on pp. 277-8, on the effect of the phytic acid in cereals in restricting the absorption of calcium, not only demonstrated one of the reasons for this deficiency but pointed a way to remedying it, which was quickly implemented by the inclusion of extra calcium in the National flour. The decisions to augment the sources of vitamin D in the diet, as recommended by two Committees of the Council (pp. 111 and 116), and the provision of extra milk supplies for pregnant and nursing women, and for young children, were independent but complementary steps of great significance.

One measure of the success of the national feeding policy in wartime is given by vital statistics, which show that the state of the nation's health, instead of deteriorating since rationing was introduced, has been generally maintained and in many respects improved. Thus, figures published by the Ministry of Health reveal that the infant and maternal mortality rates, and the still-birth rate, reached record low levels for the country in 1944. The general death rate from tuberculosis, after showing a disturbing increase in the first two years of the war (p. 69), has declined since, and the death rate from rheumatic fever in children was much lower in 1944 than before the war. It is, indeed, in children, except as regards some forms of tuberculosis, that the general improvement in health in recent years has been most evident, and there can be no doubt that one of the main factors in this improvement has been a more enlightened national feeding policy.

Reference has been made above to the steps taken in recent years to increase the calcifying properties of the diet. An interesting pointer to the effects of these measures was provided by the surveys of the state of the

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teeth of 5-year old London County Council school children made by Lady Mellanby and Dr. Helen Coumoulos in 1943 and again in 1945, as described on p. 280; these showed a great lessening in the incidence of dental decay as compared with that recorded in a similar survey in 1929, the figures for 1945 being significantly better than those for 1943. With regard to other aspects of nutrition, investigations such as the Haemoglobin Survey (p. 102), carried out during the war period to explore the incidence of iron-deficiency anaemia in representative samples of the population after several years of rationing, revealed that in only a few sections of the community were the findings less than satisfactory, while the results as a whole, although still leaving room for improvement, appeared to be considerably better than those recorded in similar but more limited surveys made before 1939. The findings of various other wartime nutritional surveys, mostly sponsored by the Ministry of Health and summarised briefly in the Report of the Chief Medical Officer for 1939-45, were in the main equally encouraging. For the successful feeding of the country during the war years, the Ministry of Food, the Ministry of Health, the Ministry of Agriculture and Fisheries, and other Government departments deserve great credit, but credit is due in no smaller measure to all those research workers in nutritional science—many of them workers for the Council—who provided the solid structure of knowledge upon which a sound food policy could be based; the part played early in the war by the Scientific Food Policy Committee of the War Cabinet in recommending the application of this knowledge to practical problems also deserves special mention.

The Council's relationship to the Scientific Food Policy Committee of the War Cabinet

This Committee was appointed in 1940 by the Lord Privy Seal, as Chairman of the War Cabinet Committee on Food Policy, one of its principal functions being to advise on the minimal diet required to maintain health and efficiency under war conditions, with due regard to the potential availability of supplies from home and overseas, and to questions of labour, shipping space, foreign exchange and other economic factors. The President of the Royal Society was Chairman of the Committee, and Sir Edward Mellanby, the Council's Secretary, was one of its nine members, who included, in approximately equal numbers, experts in nutrition, agriculture and economics; Dr. (now Professor) B. S. Platt, of the Council's staff (p. 284), served as one of the Secretaries. In addition to many matters primarily of agricultural importance, the Committee, in the course of its work, considered the following problems: collective feeding; the economic and nutritional aspects of potatoes, bread and flour; the utilisation and canning of fruits and vegetables; the place of sugar in the diet; retail prices of foods; supplies of fats and oils; the production of yeast from molasses; the use of dried milk; the adequacy of supplies of protein; and the availability of food concentrates (for vitamins). The Committee's work was almost completed before the end of 1941. It reported frequently to the War Cabinet Food Policy Committee, and its recommendations were accepted and implemented, often with major changes in the emphasis of the country's food management, and with an important bearing on the subsequent policy of the Ministry of Food. Throughout its work, the Committee constantly referred to the Council for advice in the field of human nutrition, and, through the Council's expert Committees, for help on many problems of food technology; in advance of the introduction of general food rationing in this country, its members also had confidential access to the results of the experimental study of rationing by McCance and Widdowson which is described on p. 98.

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Standing Committee on Medical and Nutritional Problems arising out of the War

Towards the end of the work of the Scientific Food Policy Committee of the War Cabinet, it became evident that numerous questions affecting the health of the population were likely to arise in the course of the practical application of a national wartime food policy, and it was decided that the Minister of Health should be responsible for advising the Government, and other Government Departments, on such questions. A Standing Committee on Medical and Nutritional Problems arising out of the war was accordingly appointed by the Minister in May, 1941, under the chairmanship of the Chief Medical Officer; in addition to representatives of the Ministries of Health and Food, it has included nominees of the Department of Health for Scotland, the Ministries of Education, Agriculture and Fisheries, Labour, Supply, Fuel and Power; the Medical Research Council, the Agricultural Research Council and the Department of Scientific and Industrial Research (Food Investigation Board). It has dealt with a variety of nutritional problems, such as the allocation of food concentrates and milk to infants, children, pregnant and nursing women, and workers in industry; it has also considered questions relating to the nutritive value of various foods—for example, bread and flour, margarine, vitaminised oils, and milk for the artificial feeding of infants. On many of these matters it has in turn been advised by the Council and by the Accessory Food Factors Committee and the Food Rationing (Special Diets) Advisory Committee, whose work and recommendations are discussed in some detail on pp. 105-113 and pp. 113-127 below.

The Chemical Composition of Foods

A monograph entitled " The Chemical Composition of Foods ", by Dr. (now Professor) R. A. McCance and Miss E. M. Widdowson, both now members of the Council's staff, was issued by the Council in 1940 as *Special Report Series* No. 235. This gave the results of twelve years' work, begun at King's College Hospital, London, and continued in the Department of Medicine at Cambridge, on the determination of the organic and mineral constituents of most of the foods commonly eaten in Great Britain before the war; the foods were analysed both in the raw state and as prepared for the table. Measurements of vitamin content were omitted from this study, as these had formed the subjects of extensive research by other workers and by different methods. Some of the analytical data had appeared in earlier reports by Dr. McCance and Miss Widdowson (Nos. 135, 187 and 213 in the Council's Series), and these had all been re-checked for inclusion in the comprehensive monograph, though the earlier publications contained some additional information on certain points which was not reprinted.

That this formidable task of analysis amply justified the labour spent upon it, and met a widespread demand, is indicated by the rapidity with which copies of the book were sold. Three reprintings, with minor additions and alterations, had been made before 1943, and towards the end of the war period it was considered desirable to produce a second edition, incorporating data on the analysis of many different varieties of flour, and of dried egg, " Household " dried milk and other foods introduced or modified during the period of hostilities. The new edition was published early in 1946.

An Experimental Study of Rationing

From the beginning of the war, it became evident that supplies of imported foods for the population of the United Kingdom would have to be rigidly curtailed, and that some form of rationing of the available foodstuffs would

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soon need to be enforced. With this prospect in view, Dr. McCance and Miss Widdowson indicated to the Council in September, 1939, that they and a number of colleagues at Cambridge were prepared, in advance of the introduction of compulsory rationing, to subsist voluntarily for a period of weeks or months on a very restricted diet scale, suddenly imposed, in order to observe its physiological and psychological effects on healthy adults of both sexes. The experiment was duly undertaken with the Council's approval, the weekly " rations " of the volunteers being planned to correspond closely with those which might be expected to be accessible to the civilian population even under very severe blockade conditions, and which, in the light of existing knowledge, seemed likely to be the minimal needed to maintain a good level of general fitness and well-being. In many respects —such as in the amounts of meat, fats, sugar and milk taken—the experimental rations were much more restricted than those actually available for the population of this country during the war years, the blockade conditions envisaged as possible being considerably worse than those ultimately experienced. In other respects, however, the similarity between the experimental diets and the national rationing scales, adopted two years later, was striking. The volunteers were allowed unlimited quantities of bread, made of a 92 per cent. extraction flour with calcium carbonate added; potatoes and other vegetables were also unrationed in the experimental diets. The quantities of bread and potatoes consumed by the volunteers in lieu of other food were remarkable, and they obtained a large part of their energy requirements in this way. The same, no doubt, applied in the case of the general public during the war years, since potatoes then were unrationed, though sometimes in short supply, and bread rationing, even of moderate degree, was not introduced until after the end of hostilities, when the inherent dangers of the blockade were over. The effects of the experimental rations on the volunteers were assessed by biochemical and physiological tests, as well as in terms of their psychological reactions to the restricted diets. At the end of a test period of some three months, it was found that the four volunteers who had been subjected to the complete experiment were very fit, and could carry out satisfactorily, and without undue fatigue, most severe exercise tests, requiring a very high expenditure of energy.

The experiment was completed early in 1940, and its results were reported confidentially to the War Cabinet and to the various Government departments which would be concerned with problems of food procurement and of food rationing on a national scale; there is no doubt that they materially influenced subsequent policy in these regards. It was decided by Government that the report on the experiments should not be published during the war years, but a full account of the work was issued in 1946 as the Council's *Special Report Series* No. 254.

The Council recognise that to submit to a personal experiment of this kind, at a time when food rationing had not been generally introduced in this country, required a very high degree of individual discipline on the part of the volunteers, and they here pay tribute to the self-sacrifice and persistence of those who engaged so meticulously in this important and timely investigation.

Nutritional Investigations undertaken by the Council for the Service Departments.

Naval rations.—The results of the investigations of Army rations undertaken before the war by members of the Council's staff, at the request of the War Office (see below), were communicated also to the Admiralty and the Air Ministry. In 1940 the Council were invited by the Medical Director-General of the Navy to examine the existing scale of rations for naval ratings, especially the " daily standard ration for service afloat ". On the basis of

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advice given by the Council's experts, various suggestions for improvements in the rations were made, with particular regard to methods of cooking green vegetables so as to preserve their vitamin C and mineral content.

Rations for shipwrecked personnel.—Following a request from the Admiralty in 1941, the Council established a Committee on the Care of Shipwrecked Personnel (p. 419). Surgeon-Vice Admiral Sir Sheldon Dudley, then Medical Director-General of the Navy, served as Chairman of this Committee, and, as well as naval representatives, it included nominees of the Air Ministry and the Ministry of War Transport, since its terms of reference extended to the hazards of the aviator brought down into the sea, and those of the men of the Merchant Navy exposed to the constant dangers of unrestricted submarine, surface and aerial warfare. Among the many problems examined by this Committee were those of appropriate rations for issue in ships' lifeboats. It was realised from the first that the greatest single factor in the preservation of life at sea after shipwreck is an adequate supply of drinking water: water is relatively much more significant than food in these circumstances, though a careful choice of suitable food rations to sustain physique and morale is also important. Many trials were made in human volunteers to determine the minimal daily intake of water needed to maintain health, and to decide the most economical way in which water could be rationed in lifeboats to secure maximum survival; acknowledgement is due in particular to Dr. W. S. S. Ladell and colleagues at the National Hospital, Queen Square, London (pp. 256-64), and to Dr. McCance, Dr. D. A. K. Black and others in the Department of Medicine at Cambridge, for their fortitude in submitting to these trying experiments. The Committee's recommendations regarding water and food rations, and many other important matters affecting the shipwrecked, were incorporated in " A Guide to the Preservation of Life at Sea after Shipwreck " (*Medical Research Council War Memorandum* No. 8), published in 1943. A very wide distribution of this pamphlet was made by the Admiralty, and it had the largest circulation of all the Council's publications during the war period.

Army rations—general.—In 1937 the Council received a request from the War Office for advice on the adequacy of the vitamin content of emergency canned food rations, both before and after storage in temperate and tropical climates. Problems relating to the vitamin C content were extensively investigated by Dr. S. S. Zilva, of the Council's staff, at the Lister Institute, London, and questions of the vitamin B_1 and vitamin A content were examined by Dr. L. J. Harris and Dr. T. Moore, of the Council's staff, at the Dunn Nutritional Laboratory, Cambridge. Brief accounts of some of these studies, and of the important practical recommendations arising from them, are given on pp. 286-7 and 292. Reports on the results were transmitted to the Service Departments in January, 1939, and the Council were thereafter invited to review the scale of Army rations in general. A special Sub-Committee on Service Rations was convened for the purpose, and after various further *ad hoc* investigations, it recommended a number of improvements, which were adopted. In the spring of 1941, the Council were asked by the War Office to arrange a survey of the current Army messing arrangements in Great Britain. This was undertaken by Dr. B. S. Platt of the Council's staff, who visited a number of Units of different types in June and July of that year. There was evidence of a need for various changes, and recommendations for the expert supervision of Army feeding arrangements were transmitted to the War Office.

Compact rations for special troops.—One outstanding problem revealed in the survey of Army feeding was the need for provision of a compact ration for special troops, such as Commandos and airborne troops. Following a conference at the War Office in 1941, a special Sub-Committee of the Military

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Personnel Research Committee (p. 134) was appointed to plan a ration of this type. Much work on the subject was done in the ensuing months by members of the Council's staff and others, and a compact ration was devised which was concluded, in tests made in Canadian troops undergoing strenuous battle training, to have a number of advantages over the War Department 2-day ration then being issued. Samples of the new ration, together with technical details of its production and packing, were submitted to the Army Council, with the suggestion that, with comparatively minor modifications, it could be adapted for use in regions of extreme cold and in the tropics. Many novel features of the compact ration recommended were ultimately incorporated in an Army standard ration.

Salt and water requirements of troops in tropical climates.—The experience gained by workers for the Council in their studies of the effects of water deprivation under conditions simulating those in ships' lifeboats adrift, and in related studies, was applied later in a field investigation, undertaken at the request of the War Office, into the water and salt requirements of troops in tropical climates. These observations were made by Dr. W. S. S. Ladell, Dr. J. C. Waterlow and Major M. Faulkner Hudson, R.A.M.C., at Shaiba in Southern Iraq in the summer of 1943. Their findings with regard to the nature and prevention of the different types of heat effects encountered were transmitted to the War Office and have since been published (*Lancet*, 1944, **ii**, 491 and 527). Other investigations into the physiology of man under tropical conditions—and into the effects of excessively hot and humid working conditions—are mentioned on pp. 142 and 258.

Feeding of R.A.F. personnel.—At the request of the Air Ministry, a survey of the arrangements for feeding Royal Air Force personnel was made early in 1941 by Dr. Platt of the Council's staff. His report stressed the need for expert advice in the planning of feeding scales, and it recommended that improved methods of catering and cooking be introduced to secure maximum utilisation of the rations. Attention was drawn to the various ways in which gross food wastage and more subtle forms of loss of nutriment could be avoided. Methods of supervising the handling of foods were proposed, and it was suggested that a nutrition expert be enrolled in the Service, to advise on dietetic subjects and to maintain contact with research workers on nutrition. These suggestions were adopted, and Dr. T. F. Macrae, of the staff of the Lister Institute, London, was appointed to a commission in the rank of Squadron Leader as Adviser in Nutrition to the Royal Air Force; he served on several of the Council's expert committees in this field, and was able to maintain close liaison with their work.

Members of the Council's research staff were associated with various investigations of the effects of vitamins on health and physical efficiency, organised by the Air Ministry or by the Council on their behalf: examples were the enquiries into the possible relationship of nutritional deficiences to gum lesions (ulcerative gingivitis) in Royal Air Force personnel, and the studies made by Lady Frankau, with a grant from the Council, of the effects of nicotinamide and other vitamin supplements on the physical efficiency and fatigability of healthy aircrew cadets (p. 322).

Nutrition of Industrial Workers

At the request of the Ministry of Labour, a survey of feeding conditions in industry was organised by the Council in 1940; it was undertaken by Dr. Platt of the Council's staff, Dr. C. C. N. Vass of St. Thomas's Hospital Medical School, and Miss M. H. Craig of King's College of Household and Social Science, London. The survey showed a need for the improvement and extension of arrangements for feeding industrial workers. It was

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recommended that canteens be staffed and administered as a State service, and that industrial concerns should achieve a prescribed minimum standard of catering; the desirability was emphasised of caterers having at least some training in nutritional science, and of their work being supervised by a staff of industrial nutrition officers.

In 1943, Dr. R. B. Buzzard, working for the Council's Industrial Health Research Board, undertook a further survey of the efficiency of industrial canteens in a group of factories mostly engaged in aircraft production. His report (unpublished) was submitted to the firms chiefly concerned, which had invited him to make the inquiry; copies were sent also to interested Government departments.

The Haemoglobin Survey, 1943

Early in 1943, as a result of discussions with the Ministry of Health, the Council appointed a Committee (p. 419) whose primary objective was to obtain evidence of the nutritional state of the people of Great Britain in the fourth year of war.

Estimation of the haemoglobin content of the blood was chosen as the main index of the nutritional state, with estimation of the protein content of the blood serum as a subsidiary examination. Haemoglobin estimation was chosen for its simplicity and because any serious, long-continued deficiency of iron or protein, separately or in combination, is reflected in diminished haemoglobin values—that is to say, in anaemia.

The method of haemoglobin estimation adopted for the survey had to be one that was generally practised, in order that pathologists all over the country could take part, and the widely-used Haldane-Gowers instrument —despite its known limitations—was chosen for the purpose. Much care was taken to ensure that calibrated apparatus and standardised procedures were used, so that the results recorded by different pathologists should be comparable. A unique feature of the survey was the testing of the accuracy of those undertaking the haemoglobin measurements, to determine their ranges of personal error in making these.

The haemoglobin levels of 13,000 adults and 3,000 children were determined, and a much smaller number of serum protein estimations was made. The results were analysed statistically according to age, sex, civil state, types of ration and other potentially relevant factors. Because of the absence of any satisfactory indices of normality for subjects of different ages, civil states, etc., the Committee could not make precise comparisons with pre-war results. They concluded, however, that the general situation revealed by this survey in the fourth year of war was reasonably good, although an effort was needed to improve still further the haemoglobin levels of young children, pregnant women and the poorer members of the population. The Committee's recommendations were transmitted to the Ministry of Health, and a detailed account of the survey was published in the Council's *Special Report Series* (No. 252, 1945).

Nutritional Problems of the Post-war Period

Post-war bread in the U.K.—The Council were represented on the " Post-war Loaf Conference " convened by the Ministry of Food in 1945, and were concerned especially with nutritional criteria on which the Conference recommended that specifications for the post-war loaf might be based.

Nutritional problems in liberated countries.—The Council participated in the work of the combined United States-United Kingdom-U.N.R.R.A. Committee on European Food Supplies.

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Reference to the help given by the Council to the Netherlands Government, and to the War Office, in regard to the treatment of cases of starvation in liberated Holland, in German concentration camps, and in prisoners-of-war in the Far East, is made in the report on the work of the Protein Requirements Committee (pp. 128-9 below).

At the end of the period under review, a special Medical Research Council Unit to study physiological and biochemical problems of severe malnutrition was sent to Germany under the direction of Professor McCance. The work of this Unit will be summarised in the Council's next Report.

The Council's relationship to the United Nations Food and Agriculture Organisation.—During the period between the two world wars, the present Secretary of the Council had been actively concerned in the pioneer work of the Mixed Committee on the Problem of Nutrition of the League of Nations, and in the nutrition work of the League's organisation. Dr. B. S. Platt represented the Council at the United Nations' Conference on Food and Agriculture at Hot Springs in 1943. The success of that Conference was due in large measure to its recognition of the science of nutrition as the essential basis on which to plan food production and food management, and the Report of the Conference quoted the experience of the United Kingdom during the war as an illustration of how effectively a considered food policy, founded on scientific knowledge, could safeguard the health of a population. Experience gained by British workers before the war in endeavouring to apply the results of nutrition research to improving the health of the peoples of Colonial territories was of undoubted assistance at this Conference to the Governments of other relatively undeveloped countries; further reference to some aspects of this work, in regard to which the Council co-operated closely with the Colonial Office, is made in the next section.

Nutritional Problems in the Colonies

In the last two Annual Reports reference was made to the assistance given by the Council to the Colonial Office in regard to the co-ordination of field surveys of nutritional problems in Colonial territories; it was mentioned that the first of these surveys was being made in Nyasaland, under the direction of Dr. B. S. Platt of the Council's staff, who had the co-operation of officers in various departments under the Nyasaland Government, and of the International Institute of African Languages. This survey was completed by the early summer of 1940, when Dr. Platt returned to England to act as one of the Secretaries of the Scientific Food Policy Committee of the War Cabinet (p. 97) and to take part in various researches on nutritional problems affecting the Fighting Services and the civilian population of the United Kingdom, as briefly recorded above. Although opportunities for intensive field studies in the Empire overseas were necessarily curtailed for much of the period under review, the Council were able to advise the Secretary of State for the Colonies on the solution of certain urgent problems of Colonial nutrition which arose during the war; these included the utilisation of alternative foods in territories where the ordinary foods became scarce, the supplementation of restricted food supplies, as, for example, in Malta and Gibraltar under siege, the feeding of Colonial troops and labour, and the preparation of estimates of food supplies likely to be needed on the re-occupation of the Far Eastern territories.

With the primary object of assisting a resumption of co-ordinated field studies of nutritional problems in the Colonies, the Council, at the beginning of 1944, established a Unit for Research in Human Nutrition (p. 284), and appointed Dr. Platt as its Director. Temporary accommodation for the Unit

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was provided at the National Hospital for Nervous Diseases, Queen Square, London, by courtesy of the authorities of that hospital. The first monograph to be published from the new Unit was in large measure an outcome of the Nyasaland survey, on which a draft report had been prepared in 1940 but could not be completed for publication during the war. It had been found necessary, for the purposes of the survey, to compile a table of food values for use in Nyasaland and other areas where similar foods were consumed. This table was used as the foundation of a more comprehensive publication, setting out, in tabular form, the nutritive value of many different native and other foods known to be eaten in tropical countries. The full set of tables was issued by the Council in 1945 as their *Special Report Series* No. 253. Other publications deriving from the work in Nyasaland, including a full account of the results of the survey, will be issued as soon as practicable.

On actively resuming nutritional investigations in the Colonial Empire, Dr. Platt visited the West Indies on behalf of the Colonial Office and the Council in 1944, and West African territories in 1945. Clinical evidences of malnutrition were collected in the West Indies, and their relationship to defects in the diet was demonstrated (pp. 284-5). In a report which has since been issued by the Colonial Office, recommendations were made of steps which could be taken to effect an immediate improvement in the nutrition of West Indian populations, as a basis for further, long-term improvements.

The existing information on nutritional problems in overseas territories, including that available in the reports submitted to the Advisory Committee on Nutrition in the Colonial Empire before the war, has been used to form plans for an increasingly wide programme of field studies in the Colonies; these plans are under consideration by the Nutrition Sub-Committee of the Colonial Medical Research Committee, lately reconstituted as a joint Committee of the Colonial Office and the Council (p. 428). Staff is being appointed to a Nutrition Field Working Party for combined practical work in a rural area in the Gambia, and it is proposed to set up a Nutrition Field Research Station in the same territory, the work of both being integrated with that of the Human Nutrition Research Unit in London.

A major factor in improving the state of nutrition in Colonial territories will be the provision of suitably trained personnel. Some progress has been made in this direction, by training staff in the Council's Human Nutrition Research Unit, for posts in the Colonies, and by giving courses of instruction in the Unit to labour and welfare officers from the Empire overseas. Instruction in nutrition forms part of the course for the Diplomas in Public Health and Tropical Medicine at the London School of Hygiene and Tropical Medicine, and the Council are glad to record that Dr. Platt, while retaining the Directorship of their Unit, has recently been appointed Professor of Nutrition in the University of London, and Head of the Department of Nutrition at the School.

Nutrition in Newfoundland

In July 1944, the Council received from the Government of Newfoundland, through the Dominions Office, a invitation for Dr. Platt to take part in a nutritional survey in that Dominion. Medical and administrative authorities there had been concerned at the apparently high incidence of tuberculosis in recent years, which it was thought might be related to undernourishment resulting at least in part from war conditions. The survey, in which a number of Canadian and U.S. experts shared, took place in August 1944, and a report on the results was published in the *Canadian Medical Association Journal* in March 1945. It indicated that deficiency conditions associated

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with lack of vitamin A, riboflavin and ascorbic acid were especially frequent in the population of St. Johns and other places on the eastern coast of Newfoundland, and that the diet of the inhabitants was inadequate in several other respects, notably in regard to calcium. As a sequel to this investigation, the Council were invited, through the Dominions Office, to send experts to Newfoundland to assist the Commission of Government in their efforts at improving the nutrition of the people, and to study problems of tuberculosis in the Dominion. For the nutritional work, the services of Dr. D. P. Cuthbertson, then a temporary member of the Council's staff, were made available to the Dominion Government in the summer of 1945; and for the tuberculosis survey the Council simultaneously lent the services of Dr. P. D'Arcy Hart (p. 69) of their staff, who was accompanied by Dr. T. O. Garland, Principal Assistant Medical Officer of the Middlesex County Council. The recommendations of these three investigators were transmitted to the Dominions Office and the Newfoundland Government. A report on the tuberculosis survey, containing the suggestions of Dr. Hart and Dr. Garland of practical measures for dealing with the problem, was published in Newfoundland under the authority of the Dominion Government in 1946, and Dr. Cuthbertson's report on nutrition in Newfoundland was issued in 1947 by the Dominions Office (H.M.S.O., London). Many of the recommendations in both reports have since been implemented.

The Work of the Accessory Food Factors Committee

The Accessory Food Factors Committee is a joint committee of the Council and the Lister Institute of Preventive Medicine; its membership is given on p. 419. During the war years, the Committee and its sub-committees gave advice, and initiated research, on many important practical questions within their fields of interest. The chief of these are summarised below.

Composition of Wartime Bread

One of the first problems to engage the Committee's attention after the outbreak of war, was the composition of the flour to be used for the nation's bread, in order to provide the most nutritious loaf possible. After consultation with the staff of the Research Association of British Flour Millers and a careful scrutiny of previous work on this subject, including the important researches organised by the Royal Society during the first world war, a memorandum was drawn up recommending that the extraction of flour used should be between 80 and 85 per cent., as representing the best compromise between a high nutritive value and an acceptably pale colour. At the same time, various members of the Committee with their colleagues undertook experimental studies of the nutritive value and digestibility of the protein, vitamins and minerals contained in a series of flours containing proportions of the wheat grain which varied from 70 per cent. (white flour) to 100 per cent. (whole wheat flour). The results of these researches confirmed the previous recommendation and showed that a flour containing about 85 per cent. of the grain, in which the germ and the finer portions of the bran were included, and from which the coarser parts of the bran were omitted, possessed a value in protein and vitamin content greater than that of white flour, and only slightly inferior to that of the less digestible whole wheat flour.

Through the further co-operation of the Research Association of British Flour Millers (later to become the Cereals Research Station of the Ministry of Food), it was shown that the commercial production of a flour of this type was technically possible with the existing machinery, and that from it

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a palatable, appetising and nutritious loaf could be made. The advice transmitted by the Council to Government, through the Scientific Food Policy Committee of the War Cabinet (p. 97), that a loaf of this type would be advantageous from the health point of view, was accepted and, under the name of National Wheatmeal, such bread was at first ordered to be issued as an alternative to the white bread, made from white flour of 73-75 per cent. extraction, which was then in use; finally, in 1942, due to the pressure on shipping space, it was forbidden to mill flour to any lower extraction than 85 per cent.

In order to obviate the risk shown to be present in flours of high extraction, of interference with calcium absorption by the large proportion of phytic acid present, the Committee recommended that a small amount of extra calcium salts should be added to this flour (14 oz. as *creta praeparata* to the 280 lb. sack, or about 3 g. per kg. flour).

To ensure the desired composition for the 85 per cent. extraction flour, the specification was laid down that the content of vitamin B_1 should be not less than 1.0 I.U. per g. (0.3 mg. per 100 g.) and that of fibre not more than 0.9 per cent. The possibility of official control, however, depended on the availability of accurate and reliable methods for the estimation of these components. The Vitamin B Sub-Committee, therefore, organised a special series of collaborative researches and developed standardised procedures for the estimation of vitamin B_1. At the request of this Sub-Committee Dr. E. B. Hughes, President of the Society of Public Analysts, directed work on the estimation of fibre content, and a suitable method was evolved for the purpose.

Except for an insignificant amount of wholemeal and brown bread, National bread made from flour of 85 per cent. extraction was the only type of bread consumed in this country from the spring of 1942 until the autumn of 1944. Its adoption caused a saving of shipping space equivalent to that necessary for the transport of 700,000 tons of wheat annually.

Tables of Food Composition

Early in the war, the Ministry of Food sought advice from the Council in regard to the vitamin content of various foods, since it had become apparent that the tables of vitamin content then used by that Department and by the Ministry of Health lacked uniformity. Miss E. M. Hume, of the Council's staff, was deputed to investigate the discrepancies; she reported that these were large and affected many items. A sub-committee of the Accessory Food Factors Committee was therefore set up to compile a set of tables of vitamin values which should command general acceptance.

At the same time, for purposes of planning imports and home production, the Ministry of Food required a simplified set of tables of all food constituents, for calculating the composition of broad classes of foods in bulk. A committee to collect this information was appointed under the chairmanship of Dr. H. E. Magee, of the Ministry of Health, and the already existing sub-committee of the Accessory Food Factors Committee collaborated with it.

When the requirements of the Ministry of Food in this regard had been met, the Ministry of Health had need of a still more detailed set of tables, for the evaluation of wartime dietary surveys. Vitamin values, and values for raw foods and for foods whose composition had changed during the war, were particularly required, to supplement the information given in existing publications. By collaboration between the sub-committee and Dr. E. R. Bransby of the Ministry of Health, the necessary values were gradually collected and put into use as fast as they became available. After final

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approval by the Accessory Food Factors Committee, the tables were published in 1945 as the Council's *War Memorandum* No. 14, " Nutritive Values of War-time Foods ". They included the results of a great number of determinations specially made for the purpose in various laboratories.

Vitamin Studies

Vitamin Standardisation

At the time of the outbreak of war, preparations were being made for a meeting of the International Conference on Vitamin Standards, which it was planned to hold at the end of 1939. These preparations included several investigations on the estimation and standardisation of vitamins A, E and D. The Vitamin E Sub-Committee organised the trials necessary for the establishment of an International Standard for vitamin E (further details are to be found in the section on Biological Standards, p. 243).

Estimation of Vitamin A

The value for the conversion factor for relating the results of spectrophotometric tests for vitamin A content with the results of biological tests (expressed in international units), had been widely discussed since the second International Conference on Vitamin Standards in 1934 fixed the figure at 1,600. In 1935 and 1937, the Vitamin A Sub-Committee had organised trials to determine the value of this factor for several different materials; these were a specimen of halibut liver oil, a concentrate prepared from it, and the U.S. Pharmacopoeia Reference Cod Liver Oil. As a result of these tests, it was recommended that the value 1,600 be provisionally retained, though the need for further data was recognised. Incidentally, the value found for the Reference Cod Liver Oil was 2,619 I.U. per g. and not the 3,000 I.U per g. officially ascribed to it. In 1938, the Vitamin A Sub-Committee planned a similar series of co-operative trials, in which nine laboratories participated, on the β-naphthoate ester of vitamin A prepared by Dr. T. H. Mead in the laboratories of the British Drug Houses, Ltd. The investigation included biological tests of the ester against the International β-carotene Standard. This work was completed in 1942, and, from the pooled results of this and the preceding tests, a figure of 1,740 was recommended for the conversion factor.

The value 1,740 is still at variance with that of 2,000 generally used in the United States, and this discrepancy may be due to the habitual use in the latter country of the U.S. Pharmacopoeia Reference Cod Liver Oil as standard. In Great Britain the International β-Carotene Standard is generally used. This difference in the conversion factors used here and in America has a commercial implication, in that the prices of vitamin A concentrates are based on figures for their potency, measured spectrophotometrically, and expressed in I.U., which naturally vary with the magnitude of the conversion factor.

Deterioration of Vitamin A in Margarine

In July, 1941, it appeared that the vitamin A potency of the vitaminised margarine then being issued as an essential part of the ration was below the scheduled value of 20 I.U. per g. In routine spectrophotometric tests of this product, Professor R. A. Morton found a loss in potency of 25 to 30 per cent. when the added vitamin A was in the free form as the alcohol, and of 10 per cent. when it was in the combined form as the ester.

Biological tests, made on the same material as the spectrophotometric ones, were necessary to determine whether or not this loss was real. A series of

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such tests was therefore planned by the Vitamin A Sub-Committee, to be made in five laboratories, with margarines containing vitamin A in one form or the other and, for purposes of comparison, with butter and a " dummy " butter. The last was prepared from a fat blend as used for margarine, with addition of vitamin A concentrate and pure β-carotene in the proportions found in an average summer butter.

The results showed that both types of margarine, and the dummy butter, had a vitamin A potency of 12 to 20 per cent. less than that expected. It was found also that with margarine containing the ester of vitamin A there was no subsequent decline of vitamin A potency, but with the margarine containing the alcohol the potency fell to 60 per cent. of the scheduled value within 6 months.

Human Requirement of Vitamin A

In view of the world shortage of vitamin A, and the conflicting reports as to the minimal amounts of it required to maintain health, the Ministry of Food, in December, 1941, applied to the Council for advice in fixing the amount of the adult human requirement in terms of vitamin A and of carotene: the matter was referred to the Vitamin A Sub-Committee. It was evident that the question could be settled satisfactorily only by an experiment on human beings.

The experiment, which was financed by the Council, was carried out at the Sorby Research Institute, Sheffield (p. 72), and lasted from July, 1942, until October, 1944. A group of 23 conscientious objectors volunteered to live on a diet designed to be as deficient as possible in vitamin A and carotene, but complete in all other respects. The diet contained no vitamin A as such, and only about 70 I.U. per head daily of the vitamin's precursor, carotene. Seven of the volunteers received the deficient diet with daily supplements of 2,500 I.U. of vitamin A, or about 5,000 I.U. of carotene in oil or from natural sources; the remaining 16 received the diet unsupplemented. Carotene was estimated for set periods in the faeces of those receiving the carotene supplements, so that the amount retained from the various sources could be determined.

The research as planned had three chief aims.—(i) to observe the early signs of deprivation of vitamin A, about which there had been much dispute; (ii) to determine the amount of the adult human requirement in terms of vitamin A; (iii) to determine the amount of the adult human requirement in terms of carotene.

Signs of deprivation.—Of the 16 individuals subjected to deprivation, none showed any signs of deficiency of vitamin A within a year. After 14, 17 and 22 months, respectively, three showed the effects described below. The remainder continued to receive the deficient diet for periods up to 2 years without showing any sign of depletion other than a slow fall in the blood plasma content of vitamin A; one after 22½ months' deprivation did not show even this.

In the three depleted subjects who showed evidence of deficiency, there was a marked fall in the plasma content of vitamin A, and deterioration of the capacity for dark adaptation. No changes in the sclera or cornea were observed with the slit lamp. Follicular hyperkeratosis occurred, but it was not specially related to the state of vitamin A nutrition. No thrombopenia was detected.

The adult human requirement in terms of vitamin A.—The evidence obtained in the experiment, and the results of a contemporaneous survey of the liver reserves of people dying from accident in Great Britain, were consistent with a value of 1,300 I.U. daily for the minimum protective dose of vitamin A

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for adults. To cover the inherent variation found in normal adults, and also differences in activity and environment, twice the minimal dose—*i.e.*, about 2,500 I.U. daily—was recommended.

The adult human requirement in terms of β-carotene.—From the evidence available, the minimum protective dose of β-carotene was assessed as being 1,500 I.U. daily. By analogy with vitamin A, the figure of 3,000 I.U. daily was put forward as the adult human requirement of β-carotene on the supposition that all of it is nutritionally " available ". Carotene, however, is badly absorbed, and is never " available " to the extent of 100 per cent. from any known source, so that the basal value of 3,000 I.U. daily must be augmented by another factor appropriate to the individual food or foods in which the carotene is supplied. The factors obtained in this experiment were: for carrots, canned, sliced or a purée, 4; for canned homogenised carrots, 1.8; for cabbage and spinach, 2.5; and for β-carotene in fat, 1.3. The undesirability of fixing any one general figure for the daily requirement of carotene is thus obvious, but if there were urgent reason for doing so, the figure suggested would be 7,500 I.U., which is three times that for vitamin A.

Human Requirement of Vitamin C (Ascorbic Acid)

During the war years there was a considerable increase in the consumption of vitamin C, partly on account of its somewhat indiscriminate use by surgeons as a routine measure aimed at promoting accelerated wound healing, and partly because ascorbic acid was taken by many healthy persons as a supposed useful supplement to their rations. This caused concern to the authorities responsible for the distribution of the limited supplies of ascorbic acid then available, and it became a matter of importance to establish with accuracy the human requirement of this vitamin. Previous estimations by authoritative bodies were widely divergent: for example, the Technical Commission of the League of Nations in 1937 had proposed 30 mg. ascorbic acid daily as the adult requirement, whereas the Committee on Food and Nutrition of the National Research Council, U.S.A., had concluded that 70-75 mg. daily were desirable.

Further, an explanation was sought for the frequent finding in nutritional surveys carried out in this country, of blood ascorbic acid levels as low as 0.2 mg. per 100 ml. (normal value about 1.0 mg. per 100 ml.). These low levels were not associated with any symptoms of vitamin C deficiency, and it was not known if they had any significance.

Accordingly it was decided to plan a critical investigation of the human requirement of vitamin C, and with this aim in view the existing Vitamin C Sub-Committee was re-organised and enlarged.

The investigation was carried out at the Sorby Research Institute, Sheffield, by a large number of workers. It was begun in October, 1944, at the close of the vitamin A study mentioned above, and terminated in February, 1946. Most of the 20 volunteers were conscientious objectors, and some of them had taken part in the vitamin A experiment. They were divided into three groups —one, of three men, receiving 70 mg. ascorbic acid daily; another, of seven, receiving 10 mg., and the last, of ten, receiving none beyond the small residual amount (about 1 mg. daily) present in the basal diet.

The first signs of deficiency appeared in those wholly deprived, after 190 to 240 days, as a goose-flesh-like appearance of the skin, associated with haemorrhages into hair follicles and with acne. Acne, present in several members of this group at the beginning of the trial, increased in extent and severity, and the lesions later became haemorrhagic. The blood ascorbic

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acid values had then fallen to 0.05 mg. per 100 ml. whole blood, to 0 mg. per 100 ml. plasma and to less than 1 mg. per 100 ml. white blood cells. During the succeeding 1 to 2 months the skin condition deteriorated and, in all but one member of the group, haemorrhages into the gums appeared. One subject, who previously had felt no disability, was taken ill 16 hours after a severe agility test, with a pain diagnosed as probably due to pericardial or myocardial haemorrhage; he recovered after receiving 5 g. of ascorbic acid. A second subject was found to be suffering from heart block and was similarly treated. In both cases there was a dramatic improvement in the skin condition and in general well-being.

When their condition had been definitely diagnosed as scurvy, six of the deprived subjects were given a dose of 10 mg. ascorbic acid daily. As a result of this treatment they showed a fairly rapid improvement. This dose was later raised to 20 mg. daily without much additional effect.

None of the three subjects who received 70 mg. ascorbic acid daily showed any signs of scurvy, and no definite skin changes were seen in those who received 10 mg. daily for 14 months. In the latter group, very low values were obtained for blood ascorbic acid; for whole blood, plasma, and white blood cells, the values were of the order of 0.08, 0.04 and 2.2 mg. per 100 ml., respectively. Blood values corresponding with the intake of 20 mg. daily, as later consumed by the subjects at first wholly deprived, were 0.1, 0.07, and 3.5 mg. per 100 ml., respectively; those corresponding with the intake of 70 mg. daily were about 1.0, 0.74, and 13 mg. per 100 ml., respectively. At the end of the trial all the subjects were given ascorbic acid in daily amounts of 10 mg. per kg. body weight. In those who previously had been receiving only from 5 to 20 mg. daily, a total of about 4 to 5 g. was required to bring the concentration in the whole blood up to 1 mg. per 100 ml.

This investigation provided an opportunity to study also the influence of vitamin C deficiency on the healing of experimentally produced wounds in man. The standard wounds included small incisions and stab wounds on the thighs of the volunteers. Examination of incised wounds 10 days after their infliction, in the subjects of the three groups, revealed no differences in the tensile strength or histological appearance of the tissues in the zone of wound healing. Wound tissue excised 21 days after infliction from subjects in the deprived group showed a lower tensile strength, and less collagen, than wound tissue taken from subjects receiving 10 mg. or 70 mg. daily. In these two last groups, healing of wounds appeared to proceed satisfactorily. In the deprived group there was no evidence of anaemia, nor of changes in pulse rate, temperature or body weight. Regarding tests of capillary resistance, and of fatigue, no statement can be made until the results have been finally analysed. The general results of the trial appear to confirm the adequacy of 30 mg. of vitamin C for the daily adult requirement, as proposed by the Technical Commission of the League of Nations in 1937, in contradistinction to the higher American figure. A full report of the whole investigation is being prepared for publication.

A tribute is due here to the courage of the volunteers who submitted to these experiments and those involving deprivation of other vitamins.

Work on B Vitamins

The Vitamin B Sub-Committee was concerned in a trial carried out on student volunteers at Heythrop (1941-1942) by Father Leycester King in collaboration with Professor R. A. Peters and the Oxford Nutrition Survey (Director, Dr. H. M. Sinclair). It was found that a reduction of the aneurin (vitamin B_1)

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content of the diet to approximately 300 micrograms daily led to rapid disappearance of aneurin from the urine, but produced no clinical effects within three months.

In association with members of the Council's Committee on Chemical Microbiology (p. 426), the Vitamin B Sub-Committee has begun a study of microbiological and other methods of estimating riboflavin, nicotinic acid and other B vitamins. For this purpose, National Standard preparations of these vitamins, presented by various donors and deposited at the National Institute for Medical Research (p. 242), are being studied by panels of workers set up by the Institute of Analysts. A number of collaborators have been engaged in assays by chemical, biological and microbiological methods, of the content of vitamins of the B group in dried yeast, dried meat, milk powder and wheat of 85 per cent. extraction. The studies, although not yet complete, show wide discrepancies between the results given by some of the newer methods and by biological tests on rats.

The Vitamin B Sub-Committee undertook an investigation in connection with the revision of the specification of aneurin for the British Pharmacopœia. Spectrographic tests were carried out on behalf of the Sub-Committee by Dr. E. R. Holiday, Dr. G. G. Gillam and Dr. T. Moore, with Professor R. A. Morton. The results, which were analysed statistically by Dr. J. O. Irwin of the Council's staff (p. 328), showed that, under defined conditions, the results of spectrographic tests could be used in the specification of aneurin.

Provision of Extra Vitamins for Children, Adolescents and Adults

Early in 1941, Dr. Helen Mackay, of the Council's staff (p. 331), drew the attention of the Accessory Food Factors Committee to a memorandum on the nutritional requirements of infants, prepared by a committee of paediatricians. This contained recommendations for increasing the supply of vitamins A, C and D, especially the last, for all infants, and for removing the existing restrictions on the sale of National Dried Milk, which at that time could be purchased for infants only on a medical certificate. These proposals were endorsed by the Accessory Food Factors Committee and communicated to the Ministry of Health, with the result that the Standing Committee on Medical and Nutritional Problems (p. 98) recommended that National Dried Milk should be freely available to all babies under one year, and that the supply of Vitaminised oil (containing vitamins A and D) should be extended to all children under 5 years of age and also, as far as supplies permitted, to the younger children of school age.

Subsequently, the Vitamin D Sub-Committee examined the appropriateness of various dosages of vitamin D for children and for adults. A précis of the available literature on the risk of overdosage was made by Miss Hume, and consultations took place with clinicians experienced in the prophylactic and therapeutic uses of vitamin D. On the basis of this information, the Sub-Committee recommended that schoolchildren should be provided with 3,500 I.U. vitamin D weekly, that the same amount would be of benefit, and without detriment, to the adult population, and that the incorporation of vitamin D in a staple food, preferably margarine, was the best way of attaining this end. It was pointed out that such action was of special importance, in view of the scarcity at that time of foods which naturally contain this vitamin.

These recommendations of the Vitamin D Sub-Committee were endorsed by the main Committee in March, 1943, and were communicated to the Standing Committee on Medical and Nutritional Problems.

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Claims for Vitamins and Minerals in Foods

In December, 1943, the Accessory Food Factors Committee considered a request from the Ministry of Food for assistance in formulating regulations under the Defence (Sale of Food) Regulations " for imposing requirements as to . . . labelling food of various kinds and for restricting the making, in advertisements of foods, of claims . . . of the presence of vitamins or minerals." It was felt that this subject needed special study, and a Vitamin Claims Sub-Committee was formed for the purpose, under the chairmanship of Professor Peters, with Dr. K. H. Coward as Secretary.

In its report, presented in March, 1944, the Sub-Committee made the following recommendations: (i) claims for vitamin, or mineral, content of proprietary foods and vitamin concentrates should be permitted only in respect of vitamins A, C, D, B_1, riboflavin, nicotinic acid, calcium, iron and iodine; (ii) the vitamin or mineral content of a food should be stated not in absolute units, but as that proportion of the daily requirement which the probable daily intake of the food would provide; (iii) for foods containing, in the amount which would ordinarily be consumed in one day, less than 1/6 of the daily requirement, no reference to vitamins or minerals should be permitted.

With regard to infant foods, the Sub-Committee considered that the matter should be considered by a special committee which should include paediatricians. As a general principle, however, it was recommended that, unless the food provided the full daily requirement of the vitamins and minerals mentioned above, the package must carry a clear statement of what supplements would be necessary.

These recommendations were endorsed by the Accessory Food Factors Committee and were communicated by the Council to the Ministry of Food.

Nutritive Value of Food Yeast

The possibility that the ordinary wartime diet in Great Britain might prove to be deficient in protein suggested the use of yeast as a supplementary source of protein foods. The production of a palatable strain of *Torula utilis* by the researches of Dr. A. C. Thaysen and his colleagues at the Chemical Research Laboratories of the Department of Scientific and Industrial Research, Teddington, led to an investigation of the nutritive properties of this material, which was conveniently available in a dried form, known as Food Yeast.

An extensive programme of work was started early in 1940. It included quantitative analyses of the different B vitamins in Food Yeast, carried out at the Dunn Nutritional Laboratory, Cambridge, by Dr. L. J. Harris and his colleagues (p. 291), and, at the Lister Institute, by Miss A. M. Copping. These analyses showed the yeast to be a richer source of B vitamins than any known food with the exception of liver.

At the Institute of Animal Pathology, Cambridge, Dr. T. F. Macrae and his colleagues showed that, when given to young pigs as a supplement to a cereal (maize) diet, the proteins of Food Yeast had a nutritive value for the support of growth equal to that of casein; however, the pigs were liable to develop rickets unless the amount of yeast given was small or codliver oil was given also. Dr. W. R. Aykroyd, at Coonoor, India, working with rats, found the protein value of Food Yeast when added to a " poor European diet ", to be equal to that of meat or milk. In human trials, Dr. Macrae showed that a daily dose of 8 to 15 g. ($\frac{1}{4}$ to $\frac{1}{2}$ oz.) could be tolerated without ill effects by adults, and a lesser amount, 5 to 8 g., by children. In addition, Dr. Dagmar C. Wilson demonstrated the good effect, as shown by an accelerated rate of increase in height and weight, of a biscuit containing

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8 g. Food Yeast given daily to a group of village schoolchildren of the poorer class. Finally, reports from Dr. W. Hughes in Nigeria showed the curative properties of a small daily dose, 4 to 7 g., when given to native communities with severe symptoms of deficiency of the B group of vitamins. A summary account of these various researches with Food Yeast was published in 1945 as the Council's *War Memorandum* No. 16.

Incidence of Goitre in Great Britain

In the course of a nutritional survey carried out by Dr. Dagmar C. Wilson among women and schoolchildren in Oxford and the surrounding villages in the early years of the war, a notable incidence of thyroid gland enlargement was revealed. This led Dr. Wilson to re-examine the geographical distribution of thyroid gland enlargement among children, especially in comparison with the data obtained in the extensive survey made for the Board of Education in 1924. She found that in certain areas where the incidence of thyroid enlargement had been high in 1924, it still remained so. Her findings were reported to the Accessory Food Factors Committee in the spring of 1943, and a Goitre Sub-Committee (p. 420) was formed, with Dr. Margaret M. Murray as Secretary, to explore the question further.

The work was greatly strengthened by the co-operation of Professor J. A. Ryle, who adopted this subject for special study at the newly formed Institute of Social Medicine at Oxford. One of his important contributions was to prescribe an objective method for estimating and recording the degree of enlargement of the thyroid gland. Previously, individual observers had tended to use varying criteria in assessing thyroid enlargement, so that their results were not fully comparable.

A further series of observations was then carried out by Professor Ryle, Dr. Wilson and Dr. Murray in selected areas of England and Scotland. These field studies were supplemented by analyses of the corresponding water supplies for content of iodine, fluorine, calcium and magnesium, carried out, respectively, by Miss B. W. Simpson at the Rowett Research Institute, Aberdeen, Dr. Murray at Bedford College, London, and Dr. R. A. McCance and Miss E. M. Widdowson at the Department of Medicine, Cambridge. The results of this survey, which are now being prepared for publication, show that the incidence of thyroid gland enlargement in certain areas in England and Scotland is sufficiently high to warrant energetic prophylactic measures, and that lack of iodine in the drinking water, and perhaps also hardness of the water, are factors associated with this abnormality. A recommendation has therefore been made for the provision of iodised salt, at least in those areas where the iodine content of the water is below a certain minimum level. A practical measure already adopted as a result of the survey is the addition of a small amount of potassium iodide to the vitamin A and D tablets officially issued for the use of expectant mothers.

Publications

A list of publications by the Accessory Food Factors Committee and its sub-committees during the war years is given on p. 406.

The Work of the Food Rationing (Special Diets) Advisory Committee

In January, 1940, the Council were asked by the Ministry of Food, the Ministry of Health and the Department of Health for Scotland to appoint an expert committee " to advise from time to time on the question whether it is necessary on medical grounds to modify or supplement rations in the case of

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invalids or other persons on special diets." For this purpose the Food Rationing (Special Diets) Advisory Committee was set up, with Sir Edward Mellanby as Chairman and Professor H. P. Himsworth as Secretary; the full composition of the Committee is given on p. 420. At every meeting of the Committee, the Ministry of Food were represented by observers, either in the person of their then scientific adviser, Professor Sir Jack Drummond, or by one of his deputies, the late Dr. A. P. Platt and Mr. L. H. G. Barton.

Organisation of Food Rationing for Invalids

Relationship of the Committee to the executive authorities.—The Committee, as an advisory body, was free to comment on policy and was independent of the executive; it was thus able to serve as a court of appeal, and to give opinions, which were generally accepted as disinterested, to the several departments it advised. The success of such a relationship depends, nevertheless, upon a high degree of co-operation and trust between the advised and the advisers, and the members of the Committee wish to place on record their appreciation of the confidence, support, and help which they received from the Government departments with which they were associated. Not only were matters referred to them without prejudice, but no relevant information was withheld and, when such information was not available, every facility to procure it was placed at their disposal.

Method of working of the Committee.—Formal meetings of the Committee were held, on the average, four times a year. At each meeting the Committee received confidentially from the Ministry of Food an estimate of the position regarding food supplies during the next quarter and a statement of any proposed change in rations. On this basis the Committee advised what amendments were necessary to the existing regulations governing rations to invalids, and forecast what further categories of patients would require to be provided for in consequence of any new restrictions. The nature and quantity of the extra rations to replace those curtailed were decided, the details of certification devised, and, when necessary, the qualifying illness precisely defined. When the Committee had insufficient information to advise on a particular problem, reference was made to the appropriate professional associations of specialists or, when the knowledge did not exist, *ad hoc* investigations were planned.

In order properly to fulfil its obligations to Government departments, the medical profession and the public, the Committee had to be able to advise without delay on the many and urgent problems presented to it. But owing to wartime difficulties of travel, and the other and heavy demands on the time of members, it was impossible to arrange meetings frequently and at short notice. A large part of the business was therefore transacted by correspondence. When an urgent matter arose, whether it was referred by a Government department, resulted from an individual application, or was brought forward by a member of the Committee, the medical facts, the relevant considerations regarding food supply, and the several possible solutions of the problem were set out in a confidential memorandum. This was circulated and the views of members requested. When, as was nearly always the case, members unanimously agreed on the advice to be given, this was transmitted to the department concerned; when opinions differed, a meeting was called to discuss the matter. In practice this proved a satisfactory and expeditious way of dealing with pressing problems, and it freed the Committee at its meetings from excessive detail, so that it could concentrate on broader issues and anticipatory measures.

Individual cases were considered by the full Committee only in so far as they created precedents or raised new issues. At first such cases were

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numerous, but, as the advice of the Committee accrued, the number which could not be dealt with on the basis of previous rulings decreased. The task of dealing with the daily inflow of individual applications was delegated by the Committee to particular members, who applied and interpreted the rulings of the main body, which exercised general supervision and required reports from time to time.

Individual applications.—It was clearly necessary, when extra rations were made available on the grounds of illness, that the existence of such illness in individual patients should be vouched for by a medical practitioner. In general this necessity was accepted by the medical profession, but in detail some difficulties were encountered. The most important of them arose from the fact that a medical certificate in support of a claim for extra rations had to be delivered at the Local Food Office. This led to the erroneous belief that the local officials were empowered to adjudicate at their own discretion on the merits of an application. In reality no such local adjudication was permitted. Individual applications fell into one of two broad groups—those which were provided for by existing regulations, and those which were claimed to be exceptions meriting special consideration. Applications in the first group were usually dealt with locally, the local officials simply issuing the authority to purchase the rations against a medical certificate giving either the diagnosis or a corresponding code number. Applications in the second group—and certificates for certain rare diseases, which, entitling the sufferers to large rations, had to be carefully scrutinised—were forwarded for the opinion of the Committee. All persons having access to the medical certificates were bound permanently by the provisions of the Official Secrets Act. In no circumstances were medical details requested from a doctor save at the behest of a member of the Committee, and, in such cases, the organisation of the Ministry of Food acted simply as a forwarding agency for confidential communications between two medical men.

To aid local practitioners in obtaining the extra rations approved for particular diseases, the Ministry of Food first inserted notices in the medical press and later sent confidential circulars to all doctors, informing them of the conditions which qualified for extra rations and the methods by which such rations could be obtained. In cases of doubt, further information could be obtained at the Food Offices, where the senior officials were kept informed by the Ministry of the categories of illness for which extra rations had been granted or refused; they were able to answer enquiries from medical practitioners on these points, thus avoiding much useless certification. But every claimant was entitled, if he thought his case exceptional, to have his application specially considered. In such circumstances he was asked to obtain a confidential statement of his case from his medical attendant for the information of the Ministry's medical advisers. Such special applications, appeals and complaints were collected in the Scientific Adviser's Division of the Ministry and then forwarded to one of the two members of the Committee who had been appointed to deal with them in the first instance: Professor H. P. Himsworth, in London, dealt with those from England, Wales and Northern Ireland; Professor L. S. P. Davidson, in Edinburgh, with those from Scotland.

The nature of these special applications varied widely. Some were for sufferers from rare diseases which had not previously been considered, many for patients with variants of illnesses for which extra rations had already been refused. Some were to provide novel forms of therapy, others therapies which had been supplanted. Whatever the nature of the application, the procedure was for each case to be considered individually, specialist advice being sought where necessary, and a written statement made of the reasons for or against granting extra rations. Throughout the period under review

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some sixty to eighty special applications were dealt with in this way each month. The average time elapsing between receipt of the application by the Local Food Office and the applicant being informed of the result was nine days, but to ensure that no patient suffered by deprivation of rations in this interval, the Local Food Executive Officer was empowered to grant extra rations at once when these were requested urgently.

The body of rulings which accumulated from these decisions on individual cases came to play an important part in the system of rationing. They served to amplify more general advice given by the Committee, and formed the main basis of the detailed schedule of illnesses provided for the Food Executive Officers in order that they might deal with local enquiries from patients and doctors.

Advice on the medical aspects of food policy.—Complementary to the Committee's function of recommending special rations for particular types of invalid was its work in advising on broader medical aspects of food policy. As medical advisers to the Ministry of Food its members were necessarily concerned with the relations of that body to the medical profession. It was their responsibility to devise medical certificates and regulations so as to cause the minimum of inconvenience to practitioners, to draft the necessary explanatory notices for the medical press, and to advise on such professional problems as arose from time to time. In these connections the Committee's independent status repeatedly proved its value.

The institution by the Ministry of Food of measures to curtail the production, or restrict the distribution, of certain manufactured foods resulted in various protests from manufacturers which, all other pleas having failed, were finally based on the alleged necessity of the particular food to invalids. It was a task of the Committee to advise upon the validity of such allegations; it also advised the Ministry upon requests to obtain licences for the importation of natural foods, such as citrous fruits, or prepared foods for invalids not manufactured in this country.

During the period of rationing, new foods were introduced and some familiar foods modified. Protests from invalids and other persons on special diets greeted each innovation, and the Ministry of Food had to be advised whether these were justified. Thus the introduction of National Flour raised fears for invalids with diseases of the alimentary tract, and the addition of a small amount of calcium carbonate to such flour elicited diverse objections. At the beginning of rationing it was the practice to wait until the particular food had been introduced, and then to consider the protests. Later, the Committee was informed of any forthcoming innovation, and was thus able to anticipate possible objections and submit them to investigation in advance.

It was inevitable that sooner or later the preventive aspect of dietetics should engage attention. Indeed, the very first business undertaken by the Committee was to advise the Ministry of Food to require, now that butter was to be rationed, that all margarine be fortified by the addition of specified amounts of vitamins A and D. With the advent of milk-rationing the whole question of the value of dietetic measures in the prevention of industrial disease was raised. But it was only later that this aspect passed from particular to general importance. When the situation was reached that supplies of certain essential foods were at a critically low level, the Committee felt obliged to scrutinise every new measure affecting the normal consumer, in order to see whether it threatened to increase the already considerable number of persons whose activity was impaired by ill-health. To this end, it had to consider the more general aspects of food policy and, on several occasions, was impelled to make strong representations against existing, or proposed,

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measures. It is worthy of record that such unsolicited advice was not disregarded, even when, as in the proposal to reduce the allowance of meat to the military services in order to maintain that to civilians, other considerations were involved.

General Principles

In general terms the primary function of the Committee could be defined as to determine the order of priority in which the claims of invalids for extra rations should be satisfied from the food available. The difficulty and extent of this task must obviously depend largely upon the state of the existing food stocks. When supplies are fairly satisfactory, and restrictions to the normal consumer few and relatively slight, exceptional provision need be made only for patients suffering from conditions, such as diabetes mellitus, which require highly specialised diets. When, however, the food supply is greatly restricted, and many essential foods are severely rationed, it is insufficient just to advise which requests for special diets are medically justifiable and which are not: the competing claims of justifiable and less justifiable applications have to be weighed. Such a degree of restrictions was rapidly reached in this country after the summer of 1940. From that stage onwards the Committee had to frame its advice with the clear knowledge that patients refused extra rations could no longer obtain unrationed foods which were nutritionally equivalent, and that concessions to one group of invalids might very well prejudice the supplies to others. It was therefore necessary for the Committee to weigh all applications most carefully, and to ensure, to the best of its ability, that the extra rations available reached those whose needs were greatest. To this end three general principles were adopted: first, that illnesses qualifying for extra rations should be precisely defined and the concession strictly limited to that precise group of patients; second, that extra rations should be granted only on the grounds of proven therapeutic necessity; third, that when it was impossible to satisfy all of several competing claims, the concession should be granted to those groups with the better prospects of recovery or which, by means of special rations, could be kept at work in full vigour. The implications and corollaries of these principles deserve further consideration.

In January, 1940, a letter from Sir Robert Hutchison, then President of the Royal College of Physicians of London, was published in the *Lancet*. On the basis of his experience as medical adviser to the Ministry of Food during the war 1914-1919, he advised the Committee, whose formation had just been announced, " to define as strictly as possible those diseases for which concessions are to be made ", and warned them that " otherwise nothing but trouble and dissatisfaction will result ". Occurrences during the previous war fully justified this view, for the diversion of food to such loosely defined categories as persons with gastritis, or those with pancreatic insufficiency, became so serious as to threaten the general system of rationing and, by permitting excessive latitude in certification, bred widespread discontent amongst applicants. Profiting by this experience, the Committee, as mentioned above, sought from the first to define exactly the illnesses which qualified for extra rations, and avoided the use of ill-defined or inclusive terms. Usually a precise term was available, but occasionally the definitions had to be descriptive, as when the Committee described the type of nephritis for which extra meat was available as " nephritis with gross albuminuria and oedema ", and thus avoided the use of the controversial terms " nephrosis " or " nephrotic stage of glomerulonephritis ". On other occasions the qualifying condition was a symptom not a disease, as in the cases of spontaneous hypoglycaemia, steatorrhoea,

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and hypoproteinaemia. Generalisations of any kind were avoided, and claims for extra rations on such broad grounds as debility, malnutrition or convalescence were not admitted. Such strictness of definition, although necessary, might savour of rigidity, but it was not without value to the practitioner. It encouraged confidence that a reasonably uniform standard of certification would be observed in practice; it protected the doctor from undue pressure to certify, by allowing the onus for refusal to be placed on the Ministry of Food. That the conditions were widely accepted as fair and reasonable is indicated by the relatively few protests received from the medical profession, and the comparatively small number of requests for special consideration.

The principle that extra rations should be granted only on the grounds of therapeutic necessity had many corollaries. It excluded applications made mainly on the grounds of rarity of the particular illness, and it led the Committee to reject applications in cases where satisfactory alternatives to dietetic therapy were available. Similarly, extra rations could not be allowed for the construction of those traditional dietaries for invalids and convalescents which, however comforting to the patient, are without known effect on the ultimate outcome of his disease. These refusals undoubtedly inflicted a measure of hardship on certain invalids, but they were inevitable if supplies were to be maintained to those whose need was greater. Still more distressing, but equally inevitable, was the declining of applications for extra rations based on compassionate grounds, most of which were made on behalf of patients with incurable diseases or for persons in extreme old age. In some instances, necessarily few, it was indicated to the Ministry of Food that their official prerogative of clemency might be exercised: such an instance was that of a child dying of leukaemia who craved for sweets. But all cases did not fall into these serious categories. By the same principle were decided applications for extra rations from eccentrics, from gourmets, from devotees of strange dietary cults, and from persons who believed that their social or public position could legitimately be taken into account.

The third principle, that, in deciding between competing claims, preference should be given to those invalids with the better prospects of recovery, or who required special rations to maintain active health and thus be able to contribute to the national effort, guided the Committee to one of its most painful and difficult decisions. In the early stages of rationing, as already indicated, it was only necessary to advise whether or not a particular claim was justifiable. Later, when food supplies were more restricted, the claims of different groups of invalids had to be considered in relation to each other. Eventually, food supplies became so curtailed that the requirements for invalids had to be weighed against the needs of the general population. This final position was reached in the autumn of 1941, when, in regard to the nation's milk supply, the full implication of the third principle was first enunciated. At that time about 50 per cent. of the milk available to the whole population was being distributed to persons with priority claims of one kind or another; the individual consumption of animal protein from sources other than milk was under 30 grammes a day; the military situation was grave, and the country had need of every able-bodied worker. After careful consideration, and with full realisation of the responsibility incurred, the Committee advised the Ministry of Food that " until the supply of milk was such as to provide a full allowance of milk daily to the working population, it would be against the interests of the national health to allow extra milk to mentally defectives and hopeless invalids at the expense of the already restricted supplies to active workers ". The continued limitation of the food supplies subsequently compelled the Committee to extend this advice

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to cover all rationed foods. It thus came about that mental and physical defectives, the insane, hopeless invalids, and the elderly were denied any concessions unless, coincidentally, they were suffering from another condition which in itself qualified for extra rations. The only exception to this grim and distasteful ruling was an extra allowance of tea to the elderly—a decision taken by the Ministry of Food on non-medical grounds.

Special Problems

After an experience extending over seven years of rationing, the members of the Committee have acquired a knowledge of rationing as applied to invalids which is probably unique. It seems desirable, therefore, to record some of the facts that have come to their attention; to illustrate the unexpected difficulties which beset the translation of dietetic theory into practice, and to set down the considerations which determined their advice on certain conditions. No attempt is made here to give a complete survey of the conditions dealt with, only an outline of the more interesting and important problems being possible.

Diabetes mellitus.—It is generally agreed that some restriction of carbohydrate intake is necessary in the diet of diabetic patients, and that, to compensate for this, extra fat and protein are necessary. For this reason, patients with diabetes mellitus were allowed two extra fat rations, two extra meat rations, a special ration of 12 oz. of cheese weekly, and a priority allowance of one pint of liquid milk daily, all in exchange for their sugar ration. Vegetarian diabetics were allowed to take their fat ration in the form of margarine made from vegetable oils, and the normal allowance of butter; in place of the extra meat and normal bacon ration, these persons were allowed 24 oz. of cheese weekly. Surprise was expressed in some quarters at the generous allowance of fat. That was provided to meet the needs of those diabetics who, by greatly restricting their intake of carbohydrate and substituting fat, can avoid, or restrict, the use of insulin. Extra sugar was available only to diabetics in ketosis, when two rations could be obtained at once in exchange for the fat ration.

Spontaneous hypoglycaemia.—This term is an obvious misnomer, for a low blood sugar level must necessarily have a definite cause; in practice it signifies hypoglycaemia in which the cause is not evident, and as such excludes those hypoglycaemias which may occur in the course of conditions such as Addison's disease and necrosis of the liver. It comprises the rare cases due to hyperinsulinism, and those more frequent cases in which, following the normal rise after food, the blood sugar drops to low levels. The diagnosis of spontaneous hypoglycaemia cannot be considered established unless estimation of the blood sugar reveals that it falls excessively, and this is the more necessary because the clinical symptoms of hypoglycaemia are not specific. The Committee felt justified, therefore, in requiring biochemical proof of the diagnosis before advising that extra rations be granted for individual cases. A blood sugar level below 60 mg./100 ml. was accepted as establishing the diagnosis. The rations available to proven cases were either those provided for diabetic patients, or two extra rations of cane sugar weekly, according to the method of treatment favoured by the medical attendant.

The steatorrhoeas.—Under this heading are included such conditions as coeliac disease, idiopathic steatorrhoea and sprue, all of which are characterised in their active phases by an excessive excretion of fat in the stools. At the present time the most widely accepted treatment for these disorders is by means of a high protein, low fat, low carbohydrate diet in the acute stage with a gradual reduction of the protein intake, and introduction of

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carbohydrate and fat, in the stage of convalescence. Two diets were therefore provided. That for the acute stage allowed four extra meat rations and two tins of skim milk powder weekly, in exchange for the normal fat ration. That for the convalescent stage allowed one extra meat ration and two tins of skim milk powder weekly, but did not require the cancellation of the normal fat ration. Later, dried bananas became available and, after preliminary clinical tests of their suitability, the Committee advised that these be granted to active cases of steatorrhoea as a variant on the restricted diets otherwise permissible, although the members were unconvinced that any real therapeutic value of bananas had been demonstrated.

In both world wars, the reduction of meat supplies to the normal consumer was one of the restrictions felt most acutely. As soon as it was announced that extra rations of meat were available for cases of steatorrhoea, numerous applications were made on behalf of cases of coeliac disease, sprue and idiopathic steatorrhoea. The number seemed out of all proportion to the general experience of the frequency of these conditions, and the Committee found it easy to believe the statement made on the basis of experience in the previous war, that if such applications were unchecked the whole system of meat rationing might be threatened. It was necessary, therefore, to take special measures to verify the diagnosis.

In general it is accepted that the degree of steatorrhoea is a useful index of the severity of the case: when this is high, stringent dietetic therapy is necessary; when lower, a diet approximating to normal can be taken with advantage. The ruling was therefore adopted that the extra rations were available only to patients with steatorrhoea, and not to those with coeliac disease, sprue and similar conditions who showed no excessive excretion of fat. It was then necessary to decide what constituted steatorrhoea, and, as a general indication, it was agreed that an excretion of 25 per cent. or more of fat in the dry weight of the stool when the patient was on a normal diet, or proportionately less when the intake of fat was restricted, could be accepted as establishing its presence. In accordance with this decision, the Committee asked that particulars of the fat content of the stools should accompany any request for extra rations on the ground of steatorrhoea. Undoubtedly this requirement proved irksome; but the objections to it came, not from general practitioners, but from physicians with all the resources of a teaching hospital at their disposal. Their objections were based, not on any reluctance to take trouble—one even went so far as to send stools to the Ministry of Food for inspection—but on the view that the personal eminence of the physicians in question should exempt their cases from such scrutiny. Clearly it was impossible for the Committee to accept this contention, for by doing so it would have been committed to a policy of drawing invidious distinctions between doctors.

Anaemia.—Two main forms of anaemia came to the Committee's attention —iron-deficiency anaemia and pernicious anaemia. Applications in respect of the former were usually for extra butcher's meat. No extra rations were allowed, however, for it was considered that such cases could be adequately treated by preparations of iron.

The applications in regard to pernicious anaemia were from patients who for one reason or another were under treatment with fresh liver. In the majority of cases, this arose simply from preference and the Committee had very little hesitation in advising refusal, for all experience has shown that treatment with fresh liver is far less efficient than the parenteral injection of liver extract. A minority of applications was based on supposed sensitivity to parenteral liver extracts, and to proven cases of this nature, fresh liver, in amounts equivalent to two extra meat rations weekly, was allowed. This

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concession was made because the procedure of desensitisation, although brief, is so exacting that it may be impracticable to a busy doctor.

Tuberculosis.—It is customary for patients with tuberculosis to receive a full diet, particularly one rich in fats. At the outbreak of war, investigations were in train at the Mundesley Sanatorium into the effects of an increased intake of carbohydrate on such cases. Arrangements were made for these trials to continue, and the Committee instituted a second investigation, at Tor-na-Dee Sanatorium, into the effects of a comparable increase in consumption of fat. The results of these two studies became available just when rationing began to be severe. They showed that fat had no advantage over carbohydrate, and further that, after two or three months on a high fat diet, the appetites of tuberculous patients declined and their weights fell, effects which did not occur on a high carbohydrate diet. Carbohydrate being available in ample quantities, the Committee elected, therefore, to hold a watching brief. To this end, it arranged for reports on the progress of patients to be obtained from sanatoria in the South, Midlands and Scotland, and it followed closely the reports from municipal authorities concerning the progress of cases under domiciliary treatment; and the relapse rate of patients discharged from sanatoria. At no time did these give grounds for disquiet, but nevertheless the Committee continued to receive representations from lay quarters, urging the granting of various extra rations to the tuberculous. The Secretary therefore sought the opinions of the Tuberculosis Association and the Joint Tuberculosis Council. At a full meeting of the Association, in May, 1943, the members unanimously expressed the view that the rations for tuberculous patients were adequate, and that there was no evidence that their health was deteriorating for lack of sufficient or appropriate nourishment. An independent enquiry by the Joint Tuberculosis Council elicited the same view. For these reasons, the only special rations allowed were two pints of liquid milk daily to cases of active (i.e. unhealed) tuberculosis, and later, when the cooking fat ration was reduced, supplies to tuberculous patients were continued at the previous level.

Burns, chronic suppuration or liver disease.—During the war, there were many investigations, in Britain and elsewhere, into the effect of high protein diets in a variety of conditions (pp. 127-30). These conditions fall into two main groups: cases of burns and chronic suppuration, in which there is a drain of protein from the body, and cases of liver disease. In general, patients in the former group are treated in hospital, but many patients with hepatitis are treated at home. Unfortunately, definite indication of the value of a high protein diet in such cases was not forthcoming until rationing had become stringent, and although the Committee realised the desirability of recommending special allowances for all such patients, the meat supply was insufficient to permit it. The utmost that could then be done was to allow two tins of skim milk powder to patients with hepatitis, and to trust that cases of burns and chronic suppuration would be able to receive diets from the bloc allocations and the spread-over of rations to hospitals. Extra rations have since been allowed to certain cases of liver disease.

Food sensitivity.—Shortly after the start of rationing in the U.S.A., the Secretary of the American Committee dealing with the rationing of food to invalids stated that the introduction of rationing had been followed by an acute outbreak of alleged " food sensitivity ". The British Committee had the same experience.

As soon as it was announced that butter was to be rationed, the Ministry of Food received innumerable applications for extra butter, based on alleged sensitivity to margarine. It seemed in the highest degree improbable that

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so many cases of this nature could exist, the more so as they were almost all drawn from a limited section of the population. Nevertheless, steps had to be taken if the rationing of butter were not to break down, and the Committee accordingly advised the Ministry of Food that extra butter should be granted only if the results of specified tests demonstrated that the patient was genuinely sensitive to margarine. An essential part of the tests was that the patient should correctly distinguish margarine from butter when the taste was disguised. Arrangements were made by which physicians with special knowledge of allergic states, would carry out the tests at a place within reasonable distance of the applicant's home. As soon as this requirement became known, the number of such applications declined abruptly. In the small number of persons who attended for tests, no clear instance of margarine sensitivity was obtained, only one applicant correctly distinguishing butter from margarine—a result within the limits of chance.

Similar complaints of sensitivity coincided with, or in some cases actually anticipated, changes in the type of flour. Fortunately, the Committee was well warned of such changes and was able, through arrangements made by the Council, to investigate the possibilities in advance. Extracts of the new flour, suitable for skin testing, were prepared and tested on persons known to be sensitive to different types of food. The evidence is still incomplete, but little support has been found for the view that a person can be sensitive to National Flour and insensitive to white flour. There was, however, ample evidence that persons giving positive skin tests to either flour might eat bread made from it with impunity. In the same way, tests were made of the various diluents, such as rye, barley, oat or potato flour, which might have to be added to wheaten flour to eke out limited supplies. Generally speaking, a much smaller proportion of persons reacted to these than to wheat, both in the ordinary population and those already known to be sensitive to wheaten flour. The procedure adopted to deal with cases of alleged sensitivity to any form of wheaten flour was to offer these persons rye flour, or, if they still insisted on claiming white flour, to provide their medical attendant with extracts made from National Flour and ask him to test their skin sensitivity to this alongside an extract of white flour. Only one subject was reported as reacting to the former and not to the latter. Applicants adducing reasonable evidence of sensitivity to one of the flours used on occasion to dilute wheaten flour, were provided with pure wheat flour. It is worthy of note that many applications claiming sensitivity to these diluents came from parts of the country where only pure wheat flour had been issued.

Throughout the whole period, the Committee received a small but steady stream of applications for special supplies of condensed milk because of alleged sensitivity to raw cow's milk. In such cases, the applicant's medical attendants were advised to order the milk to be boiled and, judging by the small number of renewed requests, this measure usually sufficed.

The general conclusion of the Committee in regard to food sensitivity is that many cases are more imagined than real. That is not to say either that the applications were fraudulent or that the applicants had no symptoms. But the influence of psychological factors in such cases is well known, and the Committee's experience seems to emphasize their importance.

Industrial hazards and diseases.—It is a popular belief that milk is of value for protecting workers in certain industries from the peculiar hazards of their jobs. Accordingly, when milk rationing was introduced, it was necessary to consider this whole question. There is at present no statutory obligation upon employers to supply milk to workers in any trade. The only legal enactment to supply food to employees while at work is contained in the pottery regulations; it relates only to women and young persons employed

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in processes of long duration, and makes no specific mention of a need to give milk even to users of lead glaze; in practice, however, milk is supplied, because it is the most convenient food. All the rest of the undertakings to supply milk are in the nature of agreements between employers and employees, or voluntary grants of an amenity; the former differ from the latter in that the provision of milk is based on the belief that it militates against a particular industrial risk, and in being formally incorporated in what are known as " Trade Rules ". Examination of the bases of these agreements showed that very few had any justification in toxicology. Many were of the nature of concessions made in compassion for working conditions which, while unpleasant, were not actually dangerous. In some instances, however, there were special grounds for thinking that the consumption of milk while at work, although not perhaps the best way of dealing with the particular health hazard, might be beneficial.

The Committee had therefore to consider each case on its merits; it clearly could not undertake to reinvestigate the whole problem of the dietetic prophylaxis of industrial disease, and had perforce to accept established practice when this appeared to be based on a reasonable possibility. Thus milk for consumption while on duty was granted to workers with lead and to those working with nitro or amino derivatives of benzene or toluene. The latter group is of particular importance because it includes workers using trinitrotoluene. The opinion that milk militated against the toxic effects of this substance had gained credence during the previous war. Accordingly milk was granted, but later it was found that, although protein appeared to reduce the toxicity of the explosive, fat increased it. The Ministry of Food were, therefore, advised to substitute for milk in these cases, a drink made from defatted cocoa, skim milk powder and saccharine.

Pregnant or nursing women, and infants.—Owing to the stringency of general rationing it became necessary to provide extra rations for pregnant and nursing mothers and, in so far as these were special allowances, they fell within the Committee's terms of reference. Provisions for the expectant mother caused little difficulty, the main need being to ensure an adequate supply of protein and vitamins. This was done by allowing her to obtain, in addition to her rations as a normal consumer, the relevant foods allowed on a child's ration book. Similarly, the nursing mother was allowed the benefit of her child's rations. The chief problem arose in relation to milk, and was due to the necessity of providing for different methods of infant feeding. The general arrangement was that mother and child together received 14 pints of liquid cow's milk weekly, seven pints being in the mother's right and seven in the child's. If the child was fed entirely at the breast, the mother thus obtained two pints of milk daily; if cow's milk only was used, a further 2½ pints weekly were obtainable on request. Full and half-cream National Dried Milk were available, and infants on this type of feeding received amounts of these appropriate to their age, in lieu of the normal allowance of liquid milk. Unfortunately, a similar surrender was not required in respect of children fed on proprietary brands of dried milk. Special provision, in the form of extra cow's milk, was made for mothers using complementary feeds of dried milk, while striving to increase their supply of breast milk.

Evaporated milk (condensed milk) was not a normal issue, and when " points " had to be surrendered to obtain it, applications for special supplies were received. Such milk was made available only for infants under the age of 12 months; for these it was obtainable immediately, for a period of one month, on receipt of the necessary medical certificate. Supplies were thus ensured to premature infants. Renewal of the concession, however, was granted only in special circumstances. This latter decision was based on the advice

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of a meeting of representatives of the Committee, the Ministry of Health, and eminent paediatricians, who stated that they considered " condensed milk an unsuitable food for normal infants and an unnecessary and often inappropriate food in many illnesses of infancy " and that they advised its being made available only because " facilities in practice may be such as to preclude the speedy application . . . of other methods of feeding ". In the light of this opinion it is interesting to record that, although many requests for renewal of this concession were received, none came from physicians on the staff of a hospital for children.

Problems of milk rationing.—The rationing of milk presented the Committee with a major problem, for while it is generally agreed that a generous supply of milk is useful in most illnesses, the amount available under the scheme was insufficient to provide extra supplies for all invalids. It was necessary, therefore, to agree that priority claims on the supply of liquid milk should be limited to patients with conditions in which a liberal intake of milk is an indispensible part of treatment. The classification of such illnesses, however, was not easy. Thus, while it is essential that milk be provided over long periods to cases of peptic ulcer, it is also desirable that it should be available to patients with numerous short-term ailments, of which gastro-enteritis, acute tonsilitis and influenza are examples. The scheme ultimately adopted was to divide the qualifying illnesses into classes and groups of relative priority. To ensure economy, the allowance of milk was adjusted to need, so that patients with illnesses in class I obtained two pints, those whose condition was in class II one pint daily; and the duration of the concession was either limited to the usual duration of the illness or required periodic renewal, and thus reconsideration, at reasonable intervals.

It is evident that when a regulation cannot be precisely framed, reliance for its proper working must be placed upon the discretion of those who control it. In a confidential letter, this position was put frankly before the medical profession, and opportunities for such discretion were deliberately provided. Thus, patients with peptic ulcer received two pints daily; cases of dyspepsia not certainly due to peptic ulceration one pint. When the scheme was put into force it was found that for every three certificates relating to the former condition there were two relating to the latter. If this latter category had not been provided, and the medical profession had not co-operated in using it, the majority of the applicants so certified would have been included in the class receiving two pints of milk daily, thereby greatly increasing the total milk consumption and constituting a serious and unjustifiable drain on supplies. In this connection the Committee wishes to record its recognition of the fact that, despite the personal pressure to which members of the medical profession must often have been exposed, they continued, in general, to exercise scrupulous care in certification. This was shown by the constancy of the milk consumption by invalids throughout the period of hostilities when food shortage was becoming progressively more severe.

It was perhaps natural that at the end of active hostilities it should have been felt that the need for economy was no longer pressing. Certainly the number of medical certificates for milk priorities increased by 40 per cent. between the end of the war in Europe and Christmas 1945, and it remained at this high level throughout 1946. This created a serious situation in the winter of 1946, when the supplies of milk had decreased because of the world shortage of cereals and the consequent limitation of feeding stuffs for the dairy herds in winter. It was, therefore, necessary to appeal to the profession again for its co-operation.

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The regulations in regard to milk allowances for invalids are of special administrative interest, because in them was applied, for the first time, the system by which the nature of the patient's illness was concealed by a code. Hitherto the Committee had been dealing with small groups of invalids, and it was possible for the communications concerning them to be both personal and confidential. But the numbers involved by milk rationing were far too great to be dealt with in this way: the applications had necessarily to be managed locally by a lay staff. The Committee had originally envisaged that this would be the duty of responsible persons bound by the Official Secrets Act, and it was a surprise to find, when milk rationing came into force, that the duty had been laid on the milk retailer. The Committee immediately protested, and later various professional organisations did likewise. As a result, the arrangement was cancelled and the Committee was asked to devise a system which would preserve professional secrecy. This was done by arranging that the different groups of illnesses qualifying for extra milk should be indicated on the medical certificates by code numbers, the key to which was circulated as a confidential document to doctors.

These arrangements for milk rationing were found to be so workable in practice that, when it later became necessary to ration soap and eggs, they were taken as a model. For convenience, a composite medical certificate was then devised, and the form of this owes much to the constructive criticism of Dr. W. J. Grant, a medical practitioner of Shrewsbury.

Problems concerning National Flour.—Reference has already been made to the volume of protest which heralded the introduction of National Flour, on the grounds that it produced "food sensitivity." The introduction of this flour also elicited protests on two other grounds: its alleged irritative effects on the gastro-intestinal tract, and the alleged baneful influence of the calcium salts with which it was fortified.

Irritative effects of the new flour were claimed mainly by patients with colitis, especially mucous colitis. Fortunately the Committee had had previous opportunity to test the suitability of National Flour for invalids. These tests had shown that it was well tolerated in all types of colitis, and could be taken with impunity also by patients with peptic ulceration. Applications on similar grounds were also received from patients with colostomies, although in their case the complaint was based on the nuisance of frequent evacuations rather than on a supposed deleterious effect on health. Many of these claims were anticipatory and rested on the misconception that the new flour had a high roughage content. The roughage content was, in truth, little greater than that of white flour, but when National Flour was first introduced it contained bran particles which were coarse and visible. Their removal with a flour dredger was advised and, judging by the absence of renewed applications, the procedure was satisfactory.

A special problem in this connection arose in regard to those infant foods which contain a considerable proportion of wheaten flour. The manufacturers maintained that National Flour could not be used in place of white flour in such products, as it would cause diarrhœa in infants. Samples of the foods in question made with National Flour were therefore obtained, and tested on alternate cases against the original foods made with white flour. No appreciable difference was revealed in tests at three children's hospitals. Accordingly the Committee advised the Ministry of Food to stop the special allowance of white flour to the manufacturers of cereal-containing infant foods. No complaints of any untoward effects from the new preparation have been received.

The proposal to add calcium carbonate to National Flour evoked another storm of protest. Diverse ill effects, ranging from the development of arteriosclerosis to nephrolithiasis, were feared. One eminent physician wrote

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alleging that he and his whole family were being poisoned by the added calcium; calcium salts were first added to flour three months after the receipt of his letter! Actually, the amount of calcium added to flour was hardly more than that needed to compensate for the amount of phytic acid it contained. The Committee, therefore, had no hesitation in advising the Ministry of Food that the addition of the proposed amount of calcium to bread would be harmless to invalids, and in publishing its reasons for this view in the medical press.

Bread rationing.—In the spring of 1946 it became evident that the world shortage of cereals was such as to make the introduction of bread rationing a possibility. An *ad hoc* Committee was therefore summoned by the Ministry of Health to devise schemes for such rationing, and representatives of the Food Rationing (Special Diets) Advisory Committee attended this. Three schemes were devised, each adjusted to progressively more severe shortages. The first scheme aimed at little more than eliminating waste, and to accustoming people to bread rationing, so that the other and more stringent schemes could be applied smoothly if necessary. Fortunately it was not necessary to apply the second and third schemes and, as invalids suffered little hardship from the first scheme, the special requirements of invalids under bread rationing presented no major problem.

Soap rationing.—The distribution of soap being a concern of the Ministry of Food, the task of advising on the allocation of extra supplies to invalids was referred to the Committee. Provision was made for four broad categories of cases; those with incontinence, including infants; those with discharges; cases requiring liberal applications of ointments; and persons who had ectoparasitic infestation. The allocation of extra soap to workers engaged in dirty occupations was in general dealt with directly by the Ministry of Food unless a medical question was involved; such an application was received on behalf of chimney-sweeps, on the ground that frequent washing was necessary to prevent the development of "soot cancer"; the request was granted because sweeps, working as individuals and not in factories, do not have the use of washing places at work.

De-rationing.—The problems which have hitherto been considered have mostly originated in the progressive restriction of food supplies. Some amelioration may be expected in time, but it is already evident that this cannot occur rapidly and completely, but rather will develop slowly and piecemeal. If, at each step, prompt advantage of the improving situation is to be taken, plans must be laid in advance so that, as and when supplies of the different rationed foods increase, distribution can be made to the best advantage. The Committee has therefore analysed all the conditions for which extra rations have been refused, and has classified them, in relation to each rationed food, according to the order of priority in which the refusals should be rescinded. This order has been determined by the relative therapeutic needs of the different applicants. Clearly, however, when the scheme of rescindment comes to be put into practice it will be subject to modification in accordance with the quantity and quality of the increases in food supply. Thus it may well be possible to satisfy all the applications for one particular food in good supply before allowing increased rations of another in short supply; or to meet the requests of a numerically small category of invalids before those of a group comprising many thousands of patients. With this proviso, the application of the scheme should ensure an equitable relaxation of the restrictions on invalids and other persons requiring special diets, and the distribution of the food available in conformity with the best needs of medical practice.

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The main work of the Committee is not yet complete at the time of writing. Many individual applications for special consideration are still being received and, although it is to be hoped that no further restrictions will require to be devised, the equally technical, but pleasanter, problem of relaxing the present restrictions will not be free from difficulty. But the Committee has still another task. During the years of rationing a great deal of information relating to dietetics has been acquired; and some of this seems worthy of preservation. Reference has already been made to the investigations into sensitivity to cereals, and into the effect of different diets upon the course of pulmonary tuberculosis. Of a similar nature were investigations, made for the Committee, into the tolerance of infants for low extraction flour, the use of bananas in the treatment of steatorrhoea, and the nitrogen balance of giants. In addition, there is much useful knowledge as to which dietetic measures are important—and which unimportant—in the treatment of different illnesses. All such information has been deliberately sought; but there is another category which has quietly accumulated. In the administration of the regulations concerning invalids the Ministry of Food have amassed a vast amount of statistical data revealing the incidence and distribution of different illnesses in this country. Most of these illnesses are not normally notifiable to the health authorities and, in consequence, opinions as to their frequency could hitherto only be conjectured from mortality rates. The stringency of rationing has, however, been such as to make it probable that practically all of the sufferers from conditions qualifying for extra rations would take advantage of the concessions allowed; and this opinion is confirmed by the close correspondence revealed by a preliminary comparison of the returns of cases of tuberculosis, a notifiable disease qualifying for extra rations, and the number of certificates for such rations in circulation at a given time. It may thus prove possible for the first time to estimate with some approximation to accuracy the local and general incidence rates of conditions such as diabetes mellitus, steatorrhoea, thyrotoxicosis, nephritis, spontaneous hypoglycaemia and peptic ulcer, and perhaps even to establish the correlation between these and the relevant mortality rates.

When this work is finished, and the scheme of de-rationing safely launched, the Committee's task will be ended; its members can then hand on the system they have devised, for the remainder of the period in which it is required, with the knowledge that, though subjected to criticism from time to time, it has proved workable in practice and has met the purpose for which it was planned.

The Work of the Protein Requirements Committee

The Protein Requirements Committee was appointed by the Council in March, 1944, under the chairmanship of Professor H. P. Himsworth, to co-ordinate, facilitate and, where requisite, to direct work in the rapidly expanding research field of protein metabolism in health and disease; its composition is given on p. 420; the first Secretary was Dr. D. P. Cuthbertson, and he was succeeded by Dr. A. Neuberger at the end of the period under review. In the previous ten years, work on problems of protein metabolism in health, in disease and after injury, had been so actively pursued in Great Britain, the United States and other countries, that the subject was beginning to approach that of the vitamins in complexity. At the outbreak of war, much information relevant to immediate problems of military medicine was already available, but the need for more became increasingly apparent as the war progressed. As a result, the Committee, during the war period, was largely preoccupied with problems of the moment, and it had to defer attention to the more fundamental aspects of the subject until later. Broadly

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speaking, its activities have been mainly concerned with the investigation of those aspects of protein metabolism, both general and particular, which influence the course and treatment of malnutrition, starvation, certain illnesses, and injuries (especially wounds and burns).

Production of Protein Hydrolysates and Amino-acids

When the Committee first met, information was urgently required on the large-scale preparation and clinical uses of protein hydrolysates and amino-acids. These promised to be of special value in the investigation and treatment of conditions which were already practical problems of major importance, or were likely to become so. Steps were therefore taken at once to encourage and improve the manufacture of such preparations in this country, and to test their biological effects.

Protein hydrolysates.—Meetings were arranged with the chemical advisers to the manufacturers of protein hydrolysates of potential value, at which problems of production were discussed, information exchanged, and investigations planned. Arrangements were made for the laboratory and clinical testing of the products. Many difficulties were encountered, and it is only now that reasonably satisfactory preparations are becoming available. Nevertheless, when starvation in liberated Europe suddenly became an urgent problem, sufficient progress had been made to enable this country to meet the demands for protein hydrolysate for trial in its treatment.

Amino-acids.—Although it is probable that, in the future, pure amino-acids will become of increasing importance both for investigations and treatment, their production on an adequate scale is only just becoming possible. The difficulties are both technical and financial. Under the stimulus of war needs, three amino-acids of special interest—methionine, cystine and lysine—were produced in quantity through arrangements made by the Ministry of Supply; members of the Committee are now engaged, in consultation with manufacturers, in arranging for the production of all known amino-acids in adequate amounts and of the requisite degree of purity. The technical problems of producing some of them are formidable, but satisfactory progress is being made. These amino-acids are required for three purposes: for microbiological investigations; for nutritional research; and for clinical trial.

Standardisation of Methods of Investigation

A pressing need was for the standardisation of methods of investigation, both biochemical and clinical. The Committee examined the methods for estimating plasma proteins, and recommended those appropriate to various purposes. The techniques for determining the utilisation of protein in various conditions were considered, and suggestions for the application of these to particular clinical problems were circulated to workers concerned.

Starvation

At the beginning of 1945 it became apparent that starvation on an unprecedented scale would be encountered on the liberation of countries previously occupied by the enemy. In expectation of this, the Committee collected and reviewed the available information on the treatment of starvation, and was thus in a position to help when the Netherlands Government officially requested the aid of the Council in regard to it. Members of the Committee proceeded to Holland to study the condition and needs of starving populations in the regions then liberated. They made recommendations to Supreme Headquarters, Allied Expeditionary Force, and were requested to make the necessary arrangements to deal with the medical aspects of the problem. At that time, favourable reports were being received from India on the use of protein hydrolysates

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in starvation, and the Committee was asked to procure these products, at short notice, in relatively enormous quantities. A meeting was arranged, to which were invited representatives of the Ministry of Supply and of the manufacturers, and the problem was put to them. Supplies of hydrolysate for 60,000 people were required to be in Holland in six weeks. It reflects the greatest credit on all concerned that this object was achieved. Supplies of hydrolysate for intravenous and oral feeding, of blood plasma, skim milk powder and vitamins, with all the apparatus for their administration, were packed in suitable units in a form ready for immediate use. Instruction on how to give these, and summaries of existing knowledge of the treatment of starvation, were also forwarded. In anticipation of a shortage of medical personnel, one hundred senior medical students were trained, and arrangements made for their transfer to wherever they were required. Since it was realised that the problems in starving Europe might be very different from those in Asiatic famines—from which the available information on the subject was mainly derived—arrangements were made for a team of research workers to follow immediately behind the advancing armies, to investigate cases as they were uncovered, so that treatment could be adjusted to the actual conditions as quickly as possible.

On the liberation of North-West Holland it was found that conditions, fortunately, were much less serious than had been feared, but there were still sufficient cases of severe malnutrition to provide opportunities for testing the various methods of treatment, and for investigations which proved of value later. Simultaneously, and quite unexpectedly, the appalling conditions in German concentration camps were disclosed, and these provided a situation demanding urgent measures for the treatment of starvation of extreme degree, and of the fevers and other illnesses associated with it. Supplies of the special materials for treating starvation were diverted to Germany, and the trained medical students, together with a special team of research workers directed by Dr. Janet M. Vaughan, were sent to Belsen camp. Much valuable information was obtained, on the basis of which the War Office directive for the treatment of prisoners-of-war liberated from Japanese prison camps in the Far East was constructed. The general conclusions as regards treatment were that protein hydrolysate by mouth had no advantages over skim milk powder, that the hydrolysates for intravenous injection then available required improvement, but that transfusion with double strength solutions of dried plasma was a valuable treatment in severely malnourished persons.

Secondary Malnutrition

Premature babies.—During the first two weeks of life the maintenance of proper nutrition in premature infants presents great difficulties. Swedish workers have reported that supplements of hydrolysed casein are of great benefit to such infants. These claims are being investigated.

Wounds, burns and post-operative states.—Before the appointment of the Protein Requirements Committee, much work had already been undertaken on the metabolic disturbances following injury. As a result particularly of the studies of Cuthbertson, supported partly by the Council before the war, it was known that after wounding, fractures, burns and operations, body protein is rapidly destroyed, and there was evidence—especially in conditions such as chronic suppuration, where the loss of protein is severe—that this might prolong the illness or even lead to death. Considerable benefit had been claimed to follow if the loss of protein were offset by increasing the intake of protein either by high protein diets, or by injecting protein hydrolysates intravenously. In connection with wartime extensions of this work, the Committee acted as a clearing-house for information, arranged conferences

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of investigators to discuss practical problems, and, wherever possible, facilitated the provision of special materials required for clinical or laboratory trial.

Experimental Investigations

It has already been indicated that, during the war, the Committee found it impossible to undertake large-scale experimental work on problems which were not of immediate practical importance; it was considered justifiable, however, to promote experimental work bearing on diseases which might arise from protein deficiencies during famine. Investigations of this type included work on the effects of protein deficiency in producing damage to the liver, the results of individual amino-acid deficiencies, and studies of amino-acid metabolism in experimental liver injury. The last group of studies has already found clinical application, and is proving valuable in the elucidation of the significance of amino-aciduria in human diseases.

The Present Position

With the end of the war the Committee became free to devote attention to more fundamental investigations. Much of the information acquired incidentally in the solution of immediate wartime problems is applicable also to those of peace. The data on starvation are relevant to the study of malnutrition in native races; those on protein metabolism in the wounded to the nutritional aspects of illness and convalescence in civil life. Efforts to encourage the production of preparations of the various amino-acids in Great Britain are being continued, as the progress of investigation in this field is largely dependent on such supplies. Having now obtained a promising protein hydrolysate for intravenous injection, the Committee has organised detailed clinical trials of its use in selected conditions. The experimental investigations initiated during the war are also being extended.

The Conservation of Human Milk

In response to a request from the Ministry of Health for advice on technical problems relating to the collection, preservation and drying of human milk, especially in order to save the lives of premature babies, the Council convened an *ad hoc* conference on the subject, and later appointed a Committee (p. 420) to examine the question in its various aspects. Existing methods of collecting and preserving surplus breast milk were reviewed, and studies of the bacteriological problems involved were made for the Committee by Dr. Joyce Wright. Research on the technique of drying human milk, involving a study of the properties of unskimmed human milk in relation to freeze-drying, were also undertaken for the Committee by Mr. C. J. Bradish at the Lister Institute, London. As a result of these investigations, the Committee concluded that, pending further technical developments, the use of the dried product could not be advocated for the supply of human milk on a national scale. The Committee was able, however, to recommend measures for providing supplies of human milk from frozen milk banks, which were considered, on technical grounds, to be practicable and safe. The Committee's findings were transmitted to the Ministry of Health, and accounts of the investigations made under its auspices have been published (*Mon. Bull. Min. Hlth, Lond.*, 1947, **6**, 74 and 78; *Lancet*, 1947, **ii**, 121).

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VI

PERSONNEL RESEARCH

" Personnel research " is an aspect of medical science which proved of outstanding significance in the recent war, though, as most of it had to be carried out under conditions of secrecy, few people knew about it at the time. Briefly, the term connotes, in relation to the Fighting Services, the study, by physiological and psychological methods, of the best means of increasing the operational efficiency, safety and comfort of sailors, soldiers and aviators under different environmental conditions, and conversely, the adaptation of ships, fighting vehicles, aircraft and weapons to the convenience and capabilities of those who have to use them.

Although the term " personnel research " is of recent origin, the type of study it describes is by no means a new conception. Important physiological work of this nature was done during the war of 1914-18, especially as regards the oxygen requirements of aviators flying at high altitudes, and since then the Service Departments have shown an increasing tendency to invoke the co-operation of research workers in the biological sciences in finding solutions to their many and varied practical problems involving the " human factor ". Much of this work has been undertaken directly for the Services, in Service establishments, but in regard to many other problems arising between the two wars, the help and advice of the Council have been sought by the Admiralty, the War Office and the Air Ministry.

Three widely different examples of such *ad hoc* investigations arranged by the Council for the Fighting Services before 1939 may be given here: the first was a study, undertaken at the request of the Admiralty, of colour vision requirements in the Royal Navy, on which a report was published in 1933; the second was the inquiry, begun in 1937, into the nutritional adequacy of canned Army rations, to which reference has been made on p. 100 above; the third was a series of vocational selection tests for special duties in the Fighting Services, carried out by Mr. E. Farmer and Mr. E. G. Chambers, working for the Council's Industrial Health Research Board. The development of vocational tests for Service and other needs in this country, and of associated tests for " accident proneness ", was largely due to these investigators, whose work on the subject has been described in previous reports of the Council and the Board; the extensions and practical applications of their studies during the recent war are mentioned on pp. 156 and 320. In many other directions, both psychological and physiological, the researches carried out for the Council and the Board with primary reference to industry have found useful application also to problems of Service personnel and equipment: industrial health research is indeed a form of " personnel research " of long established practical value.

The chief novelties in regard to personnel research during the past seven years have been the manner and scope of its development, by the appointment of special committees of Service representatives and civilian scientists to plan and direct it on a vastly expanded scale, and the setting up of a number of new establishments for its intensive prosecution; another new feature of such research during the war of 1939-45 was its specific application to the design of tanks, guns and other weapons. The first combined Service and civilian committee appointed in Britain specially to direct researches on physiological and psychological problems of Service personnel was the Flying Personnel Research Committee, established a few months before the recent

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war began. Although this was a Committee of the Air Ministry and not of the Council, Sir Edward Mellanby, the Council's Secretary, served by invitation as its Chairman, and a substantial part of its research programme, particularly in the psychological field, was entrusted to members of the Council's staff. Later, in 1940 and 1942, at the request of the War Office and the Admiralty, respectively, special committees were appointed by the Council themselves to direct programmes of research on problems affecting the Army and the Royal Navy. In addition, before the Royal Naval Personnel Research Committee was appointed, the Council, at the request of the Admiralty and in consultation with the other Services Departments, had established a special Committee on the Care of Shipwrecked Personnel; a brief account of the principal work of this Committee has already been given on p. 100; the Royal Naval Personnel Research Committee, with its much wider terms of reference, was a direct successor to this earlier Committee appointed to investigate problems of vital importance arising from the enemy's intensive submarine warfare against this country.

A brief account of the Council's contribution to the work of the Flying Personnel Research Committee of the Air Ministry is given below; it is followed by summary descriptions of the principal activities of the Military and Royal Naval Personnel Research Committees and their sub-committees. Naturally there has been close and continuous co-operation between the three Personnel Research Committees: confidential technical information and reports were freely exchanged between them during the war period, and it was found that the solutions provided by research for urgent problems affecting one Service were often readily adaptable to those of another.

It is certain that the practical recommendations arising from investigations promoted by the Personnel Research Committees contributed in no small measure to military success, and the saving of life, in the recent war: and it is already clear that, just as the methods and results of industrial health research have assisted in the solution of various Service problems, so also many of the research methods adopted to solve urgent problems affecting the Fighting Services under war conditions can be effectively applied in peacetime to the solution of numerous problems of the human factor in industry; these include not only the selection of the right worker for the right job, and the securing of the best practicable environment for the job, but also the design of machines, instrument panels, working benches and other equipment from the points of view of maximal comfort and efficiency. The principle in each case is that of suiting the job to the man, of suiting the man to the job, and of improving the man's performance.

The Contribution of the Medical Research Council to the Work of the Flying Personnel Research Committee (Air Ministry)

The Flying Personnel Research Committee was appointed by the Secretary of State for Air in January, 1939, at the suggestion of Sir Victor Richardson, who was at that time Director-General of Medical Services in the Royal Air Force. The name, and the terms of reference, of the Committee were adopted after consultation with Sir Edward Mellanby, who became its Chairman, as already mentioned. The Committee's functions were to advise on "the medical aspects of all matters affecting Royal Air Force personnel, which might conduce to safety and efficiency in flying, including research into problems associated with the scientific selection of flying personnel and into measures designed to maintain their physiological efficiency".

From the beginning, the Council's relationship to the work of this Air Ministry Committee has been close and cordial; in addition to Sir Edward Mellanby as Chairman, the civilian members of the Committee have included

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present and former members of the Council and also members of their scientific staff; members of the Council and of their staff have also served upon many of the *ad hoc* committees and sub-committees set up by the main Committee to direct research upon particular problems. In general, the co-operation between the Council and the Flying Personnel Research Committee, which persisted throughout the whole of the war period, took four main forms.

Firstly, the results of any researches carried out for the Council, whether on general medical problems or for specific war purposes, were made available to the Royal Air Force wherever they might be of service.

Secondly, numerous special investigations required by the Flying Personnel Research Committee and its sub-committees were carried out in the Council's research establishments by members of their staff. Thus, early work on various problems of high altitude flying, and on the design of suitable clothing for aircrews, was done in the Council's Neurological Research Unit at the National Hospital, Queen Square, London (p. 256): the Director of this Unit, Dr. E. A. Carmichael, served as a member of the Flying Personnel Research Committee and of several of its sub-committees, as well as later becoming Secretary of the Council's Military Personnel Research Committee. The laboratory researches sponsored by the *ad hoc* Committee on Air Sickness, of which Professor L. J. Witts was Chairman, were also carried out mainly in the Neurological Research Unit, those taking part including Dr. C. S. Hallpike, Dr. B. McArdle and Dr. J. Magladery, with help from Dr. G. L. Brown, of the National Institute (p. 203). Dr. Hallpike made valuable contributions to the reforms in R.A.F. acoustics achieved by the Otological Committee of the Flying Personnel Research Committee, of which he was a member. The late Dr. K. J. W. Craik was an active member of the Vision Committee, and he and his colleagues at Cambridge (see below) collaborated with the R.A.F. Institute of Aviation Medicine in solving a large number of operational problems concerning visual adaptation generally and dark adaptation in particular, including problems of cockpit illumination, and the positioning of instruments, as well as questions of scanning, plotting, and the design of radar displays. In addition to these investigations made for the Flying Personnel Research Committee in their own research establishments, the Council also supported relevant studies at some other centres. Thus, Dr. E. A. Goldie was appointed a member of the Council's temporary scientific staff to examine certain physiological problems of high altitude flying at Cambridge University and at the R.A.F. Physiological Laboratory, Farnborough (now the R.A.F. Institute of Aviation Medicine), and Dr. R. C. Browne had grants from the Council in Professor Witts's Department at Oxford to investigate the effects of drugs on the performance of aircraft pilots; both Dr. Goldie and Dr. Browne later joined the R.A.F. Medical Service.

Thirdly, certain members of the Council's scientific staff were seconded to the Flying Personnel Research Committee for the whole or part of the war period. Among these was a part-time member, Dr. (now Professor) A. Bradford Hill (p. 326), who became statistical adviser to the D.G.M.S., Air Ministry, during the war. The services of Mr. E. G. Chambers and Dr. R. B. Buzzard, both whole-time workers for the Industrial Health Research Board, were also lent to the Air Ministry for special duties; Mr. Chambers was entrusted with the general direction of developments of work carried out for the Royal Air Force in the Research Unit in Applied Psychology at Cambridge University, the formation of which is described below; Dr. Buzzard undertook important investigations affecting the re-posting of members of aircrews, including ex-prisoners of war who were not being immediately released from the Royal Air Force.

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Fourthly, from the time of the formation of the Flying Personnel Research Committee, the services and experience of the whole research team working for the Council in the Psychological Laboratory, Cambridge, under the direction of Professor F. C. Bartlett, himself a member of the Committee, were devoted very largely to studies made for the Royal Air Force. As the war continued, this team was strengthened and increased, and its contacts both with the Flying Personnel Research Committee and, by permission of the Air Ministry, directly with R.A.F. Operational Commands and Research Groups, became still closer. In this way workers for the Council collaborated with Air Ministry Training Research Department in devising the initial scheme of selection of aircrew, and for its development up to the time at which it became largely a routine and a matter for special administrative control. Other subjects investigated by the team under Professor Bartlett were:—the character and conditions of pilot fatigue; human factors in the causation of flying accidents; the selection and training of control personnel, and the equipment of operations rooms so as to avoid unnecessary error and loss of time in human observation; the optimal length of watch for radar operators in aircraft on anti-submarine patrol; the synthetic training of bomb aimers; the design and positioning of aircraft controls with regard to the normal range of efficiency of the human body and mind; and an experimental search for objective methods for the assessment of temperamental qualities required by flying personnel.

In 1944, the Council reconstituted their team working under Professor Bartlett at Cambridge into a special Unit for Research in Applied Psychology (pp. 154 and 319). The first Director of this Unit was Dr. K. J. W. Craik, who, as has been indicated already, was intimately concerned with many branches of Flying Personnel Research Committee activity. After Dr. Craik's death by accident in 1945, the direction of the Unit remained for the time being with Professor Bartlett himself, and the services of the Unit have continued to be available to the Royal Air Force. Much of the actual experimental work, from 1943 onwards, was carried out by the members of a special R.A.F. Unit, established at Cambridge and trained there, but the direction of that work has been almost wholly a responsibility of members of the Council's staff.

Only some of the more direct contributions of the Council to the war activities of the Flying Personnel Research Committee have been specified here. Others, arising from the Council's general research programme and from their close contacts with research organisations and individual scientists both at home and overseas, have also been significant.

Nor has the benefit all been one-sided, for the results of work carried out initially for the Royal Air Force have had wider implications not only in regard to problems studied by the other Personnel Research Committees and to problems of industry as mentioned above, but also in shedding light on certain fundamental questions of human physiology and psychology which fall within the Council's normal fields of interest. For these and many other reasons, it is a source of much gratification to the Council that they were able to share so largely in the work of this important Service Committee during the war years.

The Military Personnel Research Committee

The experience gained in the earlier months of the war, and particularly during the phase of active operations leading up to the evacuation from Dunkirk in 1940, brought to light many problems affecting the efficiency of the soldier in combat. The first problem of this nature referred to the Council by the War Office was that of ear protection against battle noise.

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As a result of the close association then developed between the General Staff and members of the Council's scientific staff, the Army Council in September, 1940, invited the Medical Research Council to advise also on forms of body protection, about which there was at this time considerable controversy. For this purpose, a Body Protection Committee was appointed under the chairmanship of Viscount Falmouth; on which representatives of the General Staff and of the Royal Army Medical Corps were invited to work with civilian scientists; the same Committee was asked to report on the desirability of using vizors for eye protection, and on the need for improvement in the design of steel helmets. The value of the work obtainable by such co-operation was quickly realised by the War Office, who requested that it should be extended to other matters affecting the fighting efficiency of the soldier. Accordingly, in 1941, the Council enlarged and strengthened the Committee by further appointments; and its name, following consultation with the Army Council, was changed to the Military Personnel Research Committee. Many different lines of investigation were undertaken, and as successive subjects for study developed, special sub-committees were appointed to deal with them. The membership of the main Committee and its principal sub-committees is given on pp. 421-3.

It should be emphasised that the functions of the Military Personnel Research Committee and its sub-committees related only to devising ways and means of ensuring the maximum safety, efficiency and comfort of the healthy soldier on active service, and in the use of different weapons of war; they were not concerned with the care and treatment of the sick and wounded, which was the responsibility of the Royal Army Medical Corps, who had the advice of other expert committees set up by the Council. Nevertheless, in regard to such problems as methods of protection against burns, there was close co-operation between the Military Personnel Research Committee and the Burns Sub-Committee of the War Wounds Committee, and Dr. E. A. Carmichael, the Secretary of the Military Personnel Research Committee, served also upon the War Wounds Committee, so as to maintain effective liaison between the two bodies. In regard to various other questions referred to sub-committees of the Military Personnel Research Committee, liaison was maintained in the same way with the Council's Brain Injuries Committee (p. 47).

Apart from the many investigations directed by its various sub-committees, which are summarised below, the Military Personnel Research Committee advised the Council and the War Office on a number of important matters of general policy. Thus, following requests from some of the sub-committees for more definite information about battle conditions, the Committee put forward a proposal that expert observers be attached to Army Headquarters in various theatres of war for the express purpose of quickly obtaining accurate scientific data about battle conditions, and of reporting on relevant physiological problems. This proposal was welcomed by the Council and the War Office, and it resulted in scientists selected by the Council being attached to Army Headquarters in Cairo, in India and at home, with a directive from the Army Council giving them facilities for entering battle zones, and reporting immediately to the Army Council and the Medical Research Council on urgent matters. These arrangements were the earliest whereby civilian scientists, temporarily given commissioned rank, were attached to battle headquarters; the practice was subsequently developed on a wider basis, and from it were evolved the Operational Research Groups established in later years. Brief reference has been made on p. 53 to the work done by Lieut.-Colonel W. C. Wilson, R.A.M.C., while directing the first Medical Research Section of this nature, which was sent to the Middle East in 1942; his colleagues, Major (later Colonel) A. L. Chute, R.C.A.M.C., and Major E. T. C. Spooner, R.A.M.C., studied a number of problems of

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operational importance, including physiological and other questions relating to tank warfare in the desert, the practical value of body armour as a protection against wounds of the trunk, and the medical aspects of parachute jumping. The reports of members of the section received special commendation from the Army Council, and the more pressing of the recommendations, particularly those with a direct bearing on human efficiency in tank warfare, were immediately implemented by the General Officer Commanding in Cairo. The reports of these observers were also of great value in guiding the subsequent reseach work carried out on behalf of sub-committees of the Military Personnel Research Committee.

In 1941, the General Staff invited assistance from the Committee in regard to problems of flame-throwers, and the Council arranged for Dr. R. B. Bourdillon on their staff (pp. 45 and 209) to co-operate with the Petroleum Warfare Board in work on this subject. By a series of experiments involving considerable personal risk, he was able to obtain accurate data on the relative efficiency of different flame-throwing devices, and to suggest means of protection against them.

Another study organised by the Military Personnel Research Committee related to radar equipment; by alteration in the design of such equipment, efficiency in operation was increased and fatigue reduced. An authoritative statement, based on careful measurements, was made on the absence of danger to the body while using such equipment.

Sub-Committee on Body Armour and Steel Helmets

This Sub-Committee developed from the original Body Protection Committee mentioned above. It began by considering the views of the General Staff as to the maximum dimensions of body armour which would be acceptable. From a study of casualties returned from Dunkirk, experiments with animals, and tests to determine the penetrability of different thicknesses of armour, a type of body armour was designed, based largely on experiments by Dr. C. S. Hallpike of the Councils' staff (p. 258). The design was accepted by the War Office, and was given a field trial in North Africa. During this work important information was obtained as to relative penetrating powers of different bullets and weapons; it was also shown that the angle of incidence of the surface of the armour to the projectile had little or no effect on the penetrating power of the missile. The research was extended to include the design of protective armour for the crews of light anti-aircraft guns.

Steel helmet design was considered, and after full consideration of the requirements of the War Office and Ministry of Supply, a new type of steel helmet was evolved; in this work Dr. G. L. Brown of the Council's staff took a leading part (p. 207). Advice was also offered regarding crash helmets for motor cyclists and parachute troops.

At the request of the War Office, data were collected regarding the value of vizors for the protection of the eyes. After carefully weighing their effects in impeding good vision against their potential advantages, the Sub-Committee advised against the wearing of vizors by troops in battle, and this recommendation was accepted by the Army Council.

Sub-Committee on Clothing

The Sub-Committee on Clothing was appointed in 1941. Many of the experiments relating to the design of suitable clothing for special troops were carried out by Dr. Bedford and his colleagues at the London School of Hygiene (p. 317); many others, described more fully later in this Report,

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by workers for the Council at the National Hospital, Queen Square, London (p. 256). On some of the problems discussed below there was close co-operation between this Sub-Committee and the Clothing Sub-Committee later set up by the Royal Naval Personnel Research Committee (p. 149). The work accomplished by the Sub-Committee is conveniently described under subject headings:—

1. *Water-Repellency Treatments.*—The relative merits of permanent and non-permanent waterproof finishes for textile fabrics came early under discussion. Experimental methods of measuring the waterproofing of wool were carried out by the Wool Industries Research Association, and standard battle-dress serge and greatcoat material were treated. As a result of various tests it was found that clean virgin wool was as unwettable as it was possible to make a wool surface commercially; the water-repellent treatments then available were not recommended for application to the serge in use. Certain proprietary methods of rendering clothes water-repellent were found to have advantages, such as retention of suppleness of the fabric at low temperature, and resistance to laundering and dry-cleaning. At the request of the Sub-Committee, which included representatives of the Ministry of Supply, the British Cotton Industry Research Association and the Wool Industries Research Association collaborated in redrafting the Ministry's specifications for waterproofing.

2. *Clothing for Despatch Riders.*—Since the clothing issued to Army Despatch Riders early in the war was found to give poor protection from the weather, the Sub-Committee recommended various improvements, many of which were later adopted.

3. *Clothing for Anti-aircraft Gunners.*—It was considered desirable that the garments issued should be warm, water-repellent, flexible, strong, but not too bulky, and should permit men to sleep comfortably in their working clothes. The Wool Industries Research Association produced a double-pile woollen fabric which possessed high thermal insulation values and excellent water-shedding properties. During the discussions on this subject, reference was made by the War Office representative to the need for providing protection against cold for the A.T.S. personnel working on gun sites. Following trials with various materials and designs, suitable woollen pile smocks were recommended, as well as special boots, stockings, gloves and additional underwear. These recommendations were accepted by the War Office.

4. *Clothing for Tank Crews.*—In association with workers in the Physiological Research Laboratory at Lulworth (see p. 140), a variety of designs of suits intended for use by the Royal Armoured Corps was tested. In collaboration with officers with field experience of tank warfare, a denim working overall and a tank oversuit were designed, and models were submitted for trial. As a result of these tests, and in the light of information as to the supply situation of specially woven fabrics, a special committee set up by the Quartermaster-General approved revised specifications for clothing for tank crews; sufficient numbers of the new garments were available in time for the landing in Normandy and the subsequent phases of the campaign in Europe, where they proved very satisfactory.

Researches leading to the development of a " ventilated suit " for the use of tank crews under tropical conditions are noticed separately, on pp. 142 and 260.

5. *Arctic Clothing.*—At the request of the General Staff, the equipment designed for use in cold climates was considered in detail. As the issue of this clothing was a matter of urgency, the Sub-Committee reported that

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it could be considered satisfactory for immediate needs, though certain modifications would be advantageous. In relation to this problem, tests were carried out with various types of vests used with the Brynje system of clothing for cold weather.

6. *Economy in the Use of Textiles.*—Through the medium of the Sub-Committee, scientists working in the field of cotton and woollen textiles were able to advise the War Office on ways and means of saving material during the manufacture of clothing, and on methods of ensuring appropriate salvage and repair of clothes and boots.

Sub-Committee on Weapons (Biological Assay)

This Sub-Committee, appointed in 1941 at the request of the Army Council, organised investigations to decide the effects of "blast" from a variety of weapons upon personnel in confined spaces, such as pill-boxes, armoured fighting vehicles, and buildings converted for defensive purposes. It was determined that explosions occurring outside armoured fighting vehicles in such a manner as not to cause any breach in the protective wall, entailed no significant danger from blast to personnel in the closed vehicle. Special trials with more formidable explosives showed that blast injuries in these circumstances were likely to be limited to ruptured ear drums, and damage due to displacement of the body; the risks of injury caused by fragments of armour plate would be much greater. Tests on concrete pill-boxes showed that the open embrasures did not concentrate the blast waves upon the body of a gunner operating behind the embrasure. An assessment of the effects of certain types of grenades was undertaken, and from the information made available it was apparent that the danger to life from blast due to these weapons was negligible, while from other trials it was possible to indicate that earphones gave a substantial degree of protection to the eardrums.

Entomological Sub-Committee

An early task undertaken by this Sub-Committee was the investigation of insecticides for use against lice. Following trials in this country, Professor P. A. Buxton carried out experimental work in the Middle East, the results of which demonstrated the superiority of lauryl thiocyanate and certain proprietary thiocyanates, the lethanes, to the insecticides then available against lice. New mosquito repellents were investigated in West Africa on behalf of the Sub-Committee, and simple appliances for their application under field conditions were devised. These appliances were at that time for use chiefly with repellents and insecticides containing pyrethrum. The latter, grown in Kenya, was being shipped to this country for extraction, but, at the suggestion of the Sub-Committee, the Ministry of Supply erected an extraction plant in Africa, thereby saving shipping space. The danger of mosquitoes, infested with various diseases, reaching virgin countries by aeroplane transport was brought to the attention of the authorities in this country and in the Dominions, who implemented the suggestion to tighten vigorously the control of aeroplane disinfestation. With the advent of DDT the work of the Sub-Committee lessened, and it was eventually taken over by a committee of the Ministry of Supply.

Sub-Committees on Airborne Troops and on Motion-sickness

The work of the Sub-Committee on Airborne Troops and on Motion-sickness was closely co-ordinated with that done for the Air-sickness Committee of the Flying Personnel Research Committee (p. 133); moreover, the

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fields of interest of the Sub-Committee on Airborne Troops overlapped with those of the Clothing Sub-Committee (above) and the Sub-Committee on Rations (pp. 100 and 140).

A matter of joint concern to the three Fighting Services was the question of the most practical methods of combating motion-sickness (e.g. sea-sickness and air-sickness), such as may occur in sea-going vessels and in airborne gliders and aeroplanes. Following a request from the staff of Combined Operations for information on this subject, laboratories were equipped at the National Hospital (p. 256) for a study of the physiological mechanisms involved; an account of these investigations, with the names of those who took part both in the fundamental work and in subsequent tests of potential remedies for motion-sickness, is given on p. 258, and the results need only briefly be summarised here.

By means of a swing apparatus, subjects prone and resistant to motion-sickness were carefully studied; a finding of special interest was that, in the absence of properly functioning aural labyrinths, motion-sickness could not be produced. Trials were made of various pharmaceutical preparations which had been recommended for sea- and air-sickness, and it was shown that the most potent preparation tested contained hyoscine. By arrangement with the Admiralty and the War Office, field and sea trials were organised, which workers for the Council designed and attended; these trials further demonstrated the value of hyoscine for preventing motion-sickness; similar tests carried out in gliders, with the co-operation of the Flying Personnel Research Committee of the Air Ministry, also showed the value of this substance. Subsequent experience in the British and United States Forces has substantiated the correctness of the recommendations made to the Service Departments on the basis of these and other tests.

Sub-Committee on Vision

This Sub-Committee worked in close liaison with the Vision Committee of the Air Ministry's Flying Personnel Research Committee (p. 133). An important part of its programme related to means of preserving the state of dark-adaptation necessary for night vision, while still permitting adequate map-reading at night; the need for special training in the use of night-vision was urged.

In association with members of the staff of the National Physical Laboratory, a series of experiments was instituted into the value of glare and dazzle as an offensive and defensive measure; a detailed report on the experiments was made to the War Office. Much of the other work of this Sub-Committee came into the purview of the Armoured Fighting Vehicles Sub-Committee (see below).

Sub-Committee on Analeptic Substances

Studies of the effects of giving analeptic drugs to R.A.F. personnel under different Service conditions were carried out as part of the programme of the Flying Personnel Research Committee of the Air Ministry (p. 132). In response to a request from the War Office in 1941 for advice on the value of analeptic drugs as a means of increasing fighting efficiency of soldiers, a special Sub-Committee of the Military Personnel Research Committee was appointed to consider the question, and to plan any necessary experiments. It was decided that the information then available was insufficient on which to base recommendations to the War Office regarding the uses of amphetamine (" Benzedrine ") and related to substances in military personnel, and that field trials were essential. For this purpose, observers were at first attached to British Army establishments during large-scale

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manoeuvres: however, the inability to obtain satisfactory controls, or to establish good experimental conditions during routine manoeuvres, made it necessary for a special trial to be made, for the sole purpose of evaluating this form of medication as a method of overcoming fatigue. The Canadian Army willingly co-operated, and, in consultation with the Sub-Committee, special field exercises were designed to that end. At these trials, it was shown that a single dose of 5 mg. of amphetamine, or a 5 mg. dose repeated once, caused no appreciable improvement in the capacity of the troops to carry out long marches during the day and night, to dig themselves in, and to use weapons, even though moderately severe fatigue was induced by the nature of the exercise. Other trials, carried out in Scotland, showed that 10-15 mg. of amphetamine caused increased wakefulness in fatigued men, but that there were wide individual variations in the response to this drug and to the related analeptic " Methedrine ", limiting their usefulness and safety. After full consideration of the evidence from various sources, the opinion was expressed that drugs of the amphetamine type should not be administered to soldiers for their analeptic action without a test dose having been previously given, but that these substances might be useful in helping fatigued troops whose task was known to be terminating within a matter of four to five hours, or whose task was of such a character that hope of survival was negligible except by a supreme effort. The War Office subsequently issued a directive on the permissible uses of analeptics, whcih tallied closely with the recommendations of the Sub-Committee.

Sub-Committee on Accidents to Army Vehicles

At the request of the War Office, a special Sub-Committee was set up to investigate the problem of Army traffic accidents involving wheeled vehicles. A review was made of the methods used in the training and selection of drivers, and existing Army accident statistics were carefully examined; a special survey was also made of current accident experience. Dr. A. Bradford Hill (p. 326) was largely concerned with this work. From a study of the data thus obtained, the Sub-Committee was able to recommend measures to deal with the problem. These recommendations, involving revised methods of recording accidents, and the appointment of accident prevention officers, were embodied in a report submitted to the War Office.

Sub-Committee on Rations

The work of this Sub-Committee has been mentioned under the heading of " Nutrition in Wartime " (pp. 100-101).

The Physiological Research Laboratory, Lulworth: Sub-Committee on Armoured Fighting Vehicles

In October, 1940, the Council approached the Directorate of the Royal Tank Corps through Brigadier C. G. Ling, the representative of the Army Council on the Body Protection Committee, with the offer to establish a research team for investigating physiological problems having a bearing upon the fighting efficiency of the crews of armoured fighting vehicles. This offer, readily accepted by General Pope and the Army Council, led to a very important development—namely, the establishment by the Medical Research Council of a Physiological Research Laboratory in the Gunnery Wing of the Armoured Fighting Vehicle Training School at Lulworth, Dorset. At the same time, an Armoured Fighting Vehicles Sub-Committee of the Military Personnel Research Committee was appointed, whose membership included representatives of the Directorates of Armoured Fighting Vehicles, of the Royal Army Medical Corps,

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and of the Ministry of Supply, as well as scientists nominated by the Council; Sir Edward Mellanby was the Chairman. The functions of the Sub-Committee included the defining of problems for study by the research team at the Lulworth Laboratory, the securing of necessary inter-departmental co-operation, the assessment of results, and the transmission of practical recommendations direct to the Departments and Directorates concerned.

The first Director of the Council's Laboratory at Lulworth was Dr. O. M. Solandt (p. 188), who served in this capacity in 1941-42, before taking over other important duties on behalf of the Ministry of Supply; he was succeeded by Professor I. de Burgh Daly, temporarily seconded to the Council's service by the University of Edinburgh, who in turn was succeeded, in 1945, by Dr. E. E. Pochin (p. 249); Dr. Pochin had worked with the team at Lulworth since 1941. For a brief period between the appointments of Dr. Solandt and Professor Daly, Dr. G. L. Brown took charge of the Laboratory. Other members of the staff of the Laboratory during the whole or parts of the period covered by this Report included Dr. R. M. Mayon-White, Dr. J. A. B. Gray, Dr. J. A. V. Bates and Dr. P. Hugh-Jones. Major (later Colonel) A. L. Chute (p. 135) was seconded from the R.C.A.M.C. to work in the Laboratory; Captain H. B. Wright, R.A.M.C., and Captain R. D. Harkness, R.A.M.C., also worked as members of the team. In addition, Lieut. P. H. Garrard, R.A.M.C., and Lieut. B. M. Wright, R.A.M.C., worked with the team for short periods.

The chief problems investigated at the Laboratory and in associated field studies are reviewed below under subject headings.

Fume Hazards.—One of the earliest questions examined was that of the danger to health and efficiency arising from a concentration of toxic gases inside an armoured fighting vehicle (A.F.V.), resulting especially from the firing of Besa machine guns. Improved methods of ventilation were devised to deal with this danger, and a routine method of testing all new types of A.F.V. and their weapons was finally agreed upon, as well as the maximum concentration of the noxious gases permissible. These decisions were based upon a large number of gun-fume trials, in which samples of the air at various points in a vehicle were tested for concentration of carbon monoxide and other noxious gases: samples of blood taken from the various members of the experimental " crew " of an A.F.V., usually members of the research team, were tested for carboxyhaemoglobin content. Such trials were carried out under conditions laid down by the Armoured Fighting Vehicle Directorate, and with rates of fire considered by the authorities to be representative of those occurring in action against the enemy. In the task of designing proper ventilation the team had the co-operation of Dr. T. Bedford (p. 317) and others, and much help from a firm of Heating and Ventilating Engineers. Ultimately it was found possible to evolve a satisfactory ventilating system for each new type of armoured fighting vehicle produced during the war. As this hazard arose from fumes consequent on the firing of guns, investigations were carried out to determine the actual source of the fumes within the mechanism of the gun itself; they led to proposals for alterations in the design of guns, and for improved methods of disposing of the spent shell cases and cartridges.

Fume hazards were also found to arise from the ineffective disposal of exhaust fumes. In sea-craft designed as tank landing ships, these hazards were very great, and practical trials showed that the crews of several vehicles carried in such craft had a dangerous level of carboxyhaemoglobin in their blood. This information was brought to the immediate notice of the Admiralty, who accepted the need for making arrangements for the better disposal of exhaust fumes, and for a more strict and elaborate landing drill, both designed to minimise the danger.

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Consideration of fume hazards is not complete without some mention of the potential threat of chemical warfare. This was essentially the province of the Chemical Defence Research Experimental Station of the Ministry of Supply at Porton, but workers at the Station were interested in the possibility of applying the new ventilation systems, devised to control gun-fumes, to combating dangers from chemical attack. Collaboration between the authorities at Porton and the team at Lulworth led to the suggestion of positive pressure ventilation as a solution not only to gun-fume hazards, but also to some of those of chemical warfare and of submersion.

Environmental problems.—It was realised by the Sub-Committee, and by members of the Council's staff at Lulworth and their co-workers, that the crews of armoured fighting vehicles operating in hot dry and hot wet climates might be subjected to severe physiological strain through the increase in temperature and humidity within a vehicle. Studies were therefore begun, early in 1942, to determine the effect on physical efficiency of wearing army clothing (including gas-protective clothing) on personnel at work in environments similar to those occurring in the North African Desert and the Far East. The work output of different members of a tank crew under conditions simulating battle was determined, and similar work conditions produced in specially equipped laboratories at the National Hospital (p. 258) and elsewhere; some aspects of this question were studied at the National Physical Laboratory, by arrangement with the Department of Scientific and Industrial Research. It was early established that under conditions such as those in the pre-monsoon period, the heat and humidity within a tank might become almost intolerable, and efficiency might deteriorate. A form of " personal ventilation ", by means of specially ventilated clothing, was evolved, largely as a result of work by Dr. McArdle and Mr. J. S. Weiner (p. 260); this was found to be satisfactory, as well as economical in space and weight of machinery. Improved ventilating systems were also investigated. Subsequently, the Ministry of Supply accepted recommendations for the design both of improved ventilation of vehicles and methods of " personal ventilation " for the use of crews in the Far East war theatre.

Vision.—It early became clear that modern knowledge of lighting, and of the physiological mechanisms of vision, could be effectively applied to increasing the fighting efficiency of the crews of armoured fighting vehicles.

The interior lighting of the tanks used at the beginning of the war was found to be in various ways defective; they were insufficiently lit by day in some parts of the vehicle, and very much too bright at night, preventing the important function of dark adaptation. An improved lighting arrangement was designed, which included better positioning of the lights to avoid glare and reflection, and dimming devices to reduce the danger to night vision. Following demonstration of this new type of lighting, the Directorate of Tank Design was authorised to develop such methods, and suitable fittings were prepared in consultation with supply firms. For later production of vehicles, red lighting of instruments at the right level was advocated, and this was adopted by the Ministry of Supply. Measures were also suggested for the instruction of tank crews in the more effective use of night vision, and for this purpose a pamphlet, written by the staff of the laboratory at Lulworth, was accepted as a training manual by the War Office. As a result of this work, a member of the staff was requested by the Director of Military Training in 1945 to study methods of eye training and visual observation in use throughout all branches of Army training, and to make proposals for their development. A report was made covering the physiological principles and training of day

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and night observation and recognition, and this report formed the basis for revision of these training programmes undertaken by the Camouflage Development and Training School.

It was observed, that, in failing light, the muzzle flash of tank guns dazzled the gunners because the charge of propellants was large and not flashless, and because the gunner's line of sight passed close to the muzzle of the gun. On the basis of field experiments, the use of a simple shutter attached to the telescope was adopted, as well as a revision in the drill of firing, to include closure of the eye at the moment of firing. In these experiments the retinal area bleached by the flash was estimated; parallel investigations were made on the duration of dazzle after seeing a flash from a " point source ", and its relation to duration and brightness of the flash, to illumination, size and contrast of target. The importance of the data obtained was not confined to the immediate problem; they were of value also to the Admiralty and the Royal Air Force in relation to problems connected with the defence of merchant ships.

As bigger guns were introduced, difficulties in observation of the fall of shot arose, even in daylight, and were at first attributed to dazzle by gunflash. This seemed an unlikely explanation, and investigations established that the causes of obscuration were multiple—including dust clouds, shimmer, mechanical displacement of vehicle and telescope, and the use of defective tracer shot. The assessment of the relative significance of these various factors had important technical and operational implications.

A major problem in tank design was to provide adequate fields of visual observation for the crew without endangering their safety. This was especially necessary in the case of the commander, as it had been found that casualties among tank commanders were high, through their keeping their heads exposed in order to obtain good all-round vision during battle. Commanders had found that the vision devices hitherto supplied were inadequate. Members of the staff of the Lulworth Laboratory, notably Dr. Brown, Dr. Pochin and co-workers, proposed means of overcoming these difficulties by arranging a sufficiently close grouping of periscopes in one part of a rotating cupola so that good vision would be obtained in any direction required, but not over the whole range at once. The original conception of a ring of periscopes had emanated from the Royal Armoured Corps Experimental Wing, but the new design suggested had the advantage of ensuring that the area would be in view from a single head position, without requiring constant head movement. This design was eventually accepted by the General Staff, and put into production early enough to allow of its being used at the Normandy landings. The number of casualties to tank commanders was thereby reduced.

Fields of view from other crew positions, and from the tank as a whole, were studied, and by alteration of design and placing of periscopes, " blind spots " were minimised. The extent and places of " blind spots " in enemy tanks was also investigated and reported to the General Staff.

During this work on problems of vision it became apparent that, in the design of certain optical instruments, the need for optimum performance in dim light had not been allowed for. Workers at Lulworth, in association with Dr. Craik of the Applied Psychology Unit at Cambridge (p. 319), accordingly advocated an increase in the diameter of the " exit pupil ", and the " blooming " of the lens surfaces, of tank telescopes. The first alteration was found to give an increase of 15 per cent., during a considerable period at dusk, over the range obtainable with the then standard instrument; the proposed enlargement of the " exit pupil " was adopted in the production of new

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telescopes in 1943. The second suggestion was found in trials at Lulworth to produce a further gain of .15 per cent. in dim light, and accordingly the "blooming" of tank telescopes was accepted for production and had been started before the end of the war.

The Admiralty Research Laboratory had shown that the illumination of telescope aiming marks at night caused some obstruction to vision. Calculations on the glare effect of graticules showed that the glare arose from a physical cause in the graticule plate, rather than from a physiological cause. As telescopes had to be usable both by day and night, the thickness and display of graticule lines were matters of importance. The information obtained from experiments made at Lulworth on these problems was used in the specifications for future telescopic sights. In 1941 the British tank (telescopic) sight had a magnification of 1.9, with a sacrifice of performance at long range and in poor light. Following experiments by the Council's team of workers, it was advocated in 1942 that the magnification should be increased to three, and that, as a longer term measure, two different magnifications should be adopted, the higher power having the characteristics necessary for good night vision. No further increase of tank sight magnification was considered in this country, but in America a sight was developed which combined, on one periscopic instrument, low and high magnification of the characteristics proposed by the workers at Lulworth. Other improvements, such as the use of aspherical lenses in the eyepiece, were recommended by the Council's team.

Experiments on accuracy of aim were begun in 1943, in anticipation of certain changes in the design of telescopes, and in the light of reported experience from the Western Desert. A special point studied was the obscuration of targets by the graticule line, and the need for having no lines at the central point of aim. This led to a discussion on graticule design early in 1944, following which the "split cross" was introduced as the standard aiming mark in tank and anti-tank sighting.

The work just described was related to current instrument design through an A.C.I.G.S. Committee, formed to consider and co-ordinate sighting problems in general. This "Tank and Anti-Tank Sighting Committee" was soon afterwards resolved into separate committees on tank and on anti-tank sighting problems, respectively, on both of which members of the Council's staff at Lulworth were appointed to serve. The former committee met initially in the Laboratory at Lulworth, to receive reports on sighting accuracy, and it was subsequently constituted a General Staff Committee with wide representation. All work of the Lulworth team on the problem of tank sighting was reported through this Committee, and together with that of the Army Operational Research Group and the Admiralty Research Establishment, it was effective in guiding design. The Anti-Tank Sighting Committee also referred problems to the Laboratory for study, as a result of which recommendations for the redesign of the sights for the 2-, 6- and 17-pounder anti-tank guns, and for the 95 mm. guns, were accepted. Anti-tank gun open sights were investigated, and the design adopted was based initially on the laboratory tests made at Lulworth. These observations on tank and anti-tank gun sights soon brought to light the relative importance of the various sources of error in marksmanship, such as errors of aim, errors due to imperfect smoothness of controls, errors of dispersion of ammunition, errors due to speed of aiming, and loss of aim at the moment of firing. It was felt strongly that these different factors required more careful analytical investigation, and from this point the experimental investigations progressed in two different ways: first, there was need to give answers to specific problems raised by the Design

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Department, and, secondly, there was need to initiate research into the physiological and psychological aspects of efficient gun-laying.

Gun-laying.—In the course of studies of the physiological mechanism of gun-firing, a laboratory investigation of trigger design was undertaken, which clarified and gave quantitative values to the various factors suspected to be of importance. The term " reaction time " as used by the Services was found to include other factors than those accepted in the physiological sense; in service terms it included a lag due to stiff triggers. Experiments demonstrated that hand triggers which required a pull of 50 lb., then in use on some weapons, introduced a very considerable lag and error. Again, it was found that at the time of firing, especially with a heavy mechanism, the gunner frequently moved his eye from the telescope. As a result of these studies, a solenoid firing mechanism, operated by a hand trigger, was subsequently accepted as a standard for British tanks.

To co-ordinate investigations on the effects of movement in gun-laying, a Manual Tracking Panel was set up by the Ministry of Supply, and members of the research team at Lulworth did important work for this organisation, especially in examining the characteristics of the turret-traversing mechanism from the physiological aspect.

In a series of investigations on the precision with which the instant of co-incidence between a moving and a stationary point could be signalled, it was shown that the precision decreased with increasing rate of movement, to a point at which the inevitable variability in " reaction time " became important. These experiments, and others concerning day-to-day consistency of aim, provided valuable quantitative data on which to base conclusions regarding future tank and gun design.

Much of this work on gunnery had given insight into the problem of the acquisition of accuracy in marksmanship, and some of the apparatus evolved was obviously applicable to training devices. It is probable that in future more attention will be paid to such training devices, as a means both of initiating the student into some of the separate tasks in gun-laying, and of encouraging him by experience of good scoring.

Tank driving.—As the work of the Laboratory at Lulworth began to influence tank design, increasing attention was paid to factors which tended to limit the full efficiency of the driver. Measurements of the work output of a tank crew showed that the driver was called upon to do more physiological work than any other member of the crew, except during brief periods when the loader was actually loading the main armament. The limiting factors in driving efficiency were studied at the Laboratory under the following headings:—(A) physiological, (B) anatomical, and (C) psychological.

(A) *Physiological.*—The constant use of pedals when driving a tank pointed to the need for as light a loading of the pedals as would be consistent with reliability and ease of maintenance. To determine the maximum force a driver could exert on pedals, a special apparatus was constructed. By a series of carefully controlled experiments, it was shown that the seat-to-pedal relationship was a critical factor; the most satisfactory relationship was determined, and this knowledge was applied by those responsible for the design of future models of vehicles. From a study of the use of the clutch pedal it was concluded that the travel of a clutch pedal should be of the magnitude of 5 to 6 inches, and should not exceed 8 inches; that the loading of the clutch pedal should not exceed 300 to 400 lb., and that the form of the characteristic curve should be modified within these limits in order to prevent " riding " damage by bad drivers. Experiments concerning the characteristics of the steering sticks showed a

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need for reducing the load on the stick. It was also determined that the " pull-on " type of brake was preferable to the " push-on " type.

(B) *Anatomical.*—The special relationship of the various levers to the seat, together with the range of adjustments needed to allow for drivers of different size, were studied. Suggestions were made as to the type of driving seat, the lay-out of driving gear, and the relationship of these to vision devices used in the " closed down " position.

(C) *Psychological.*—From an analysis of accident data made available by the War Office, it was found that a considerable proportion of tank accidents resulted from errors of judgment and co-ordination, associated with factors in the design or mechanics of the vehicle, such as inadequacy of " opened up " vision, mutual dependency of steering and braking controls, suboptimal pedal design, and particular tracks allowing undue skidding. Appropriate recommendations were made.

The studies briefly reported above not only had an important bearing on the future design of tanks, but also were closely integrated with the work carried out for the Royal Naval Personnel Research Committee (p. 149) on the design of gun turrets for the Royal Navy.

When the work on tank driving was initiated it was realised that to assess correct design of seat and display of levers, anthropometric data would be required. Some useful data had been collected by similar units in the United States, but further measurements were needed, and in 1943 a survey of body measurements of the Royal Armoured Corps personnel was carried out. The data obtained, which were subsequently applied in tank design, permitted a proper allowance of " crew space ", and its utilisation to the best advantage. Dr. A. Bradford Hill (p. 326) and Dr. G. M. Morant co-operated in these anthropometric studies.

Casualties among tank crews.—In the open warfare of the Libyan Desert, fires in tanks were relatively common and burns caused an important proportion of the injuries sustained by the crews of armoured fighting vehicles in battle. To reduce these, besides improved armour and anti-fire measures, it was clear that better escape exits from the tanks were necessary. A quantitative study of the factors which effect exit time from a tank was among the investigations undertaken by expert observers in the field and in the Laboratory at Lulworth. Long and obstructed escape pathways, obstacles, badly designed hatches, heavy hatch doors, and more than one man using the same hatch, were found to be the main causes of delay. In subsequent observations, the " minimum " and " economical " size and shape of hatch for 90 per cent. of the tank crew " population " were determined. Eventually, recommendations on hatch design were made, and found practical application in new models of tanks. Heavy hatch doors were spring-loaded, storage space was altered, and practice in rapid escape advised for the crews.

Impressed by the value of such studies, and realising that there was still a lack of adequate information regarding the causes and frequency of wounds in tank personnel, the Sub-Committee on Armoured Fighting Vehicles recommended to the War Office and the Council that special investigators be sent out to Normandy to collect further relevant data in the field. The War Office supported the project, and R.A.M.C. observers proposed by the Council were attached for this specific purpose to 21 Army Group. These observers were Captain Wright and Captain Harkness (p. 141), both of whom had worked in the Laboratory at Lulworth. They found that a high proportion of men became casualties when dismounted; they noted the frequency of casualties caused through partial exposure of the body through a hatch, and

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the number associated with mechanical damage to the tank; they also analysed, where possible, the nature of the causative missile. In parallel with the survey of casualties, a study of the site or sites of damage to the tank was undertaken.

In association with the field observers in Northern Europe, Dr. Mayon-White, from the Lulworth Laboratory, carried out an investigation of the causes of wounding in casualties among tank crews returned to hospitals in this country. The high incidence of casualties amongst dismounted crews was confirmed; it was also found that the majority of injuries result from fragments, and that blast and displacement injuries were relatively unimportant. An analysis of the recovery rate of the casualties showed that burns were much the least severe forms of injury among the survivors who reached Britain, men so injured returning more often, and more rapidly, to duty than casualties of other types. A critical analysis of the data obtained gave very useful information regarding the lethal quality of various weapons, vulnerable areas of tanks, figures for rate of crew replacements, and the nature and anatomical distributions of wounds. Such data, not collected before, provided knowledge of fundamental interest not only to designers of tanks, and students of tank tactics, but also to those responsible for arranging the collection and care of the wounded.

So valuable was the work of the Armoured Fighting Vehicles Sub-Committee and the Council's research team at Lulworth found to be, that, when the United States of America entered the war, the authorities there sent representatives to report on the work at Lulworth and immediately set up an organisation with generously equipped laboratories to undertake similar studies. A most happy and useful collaboration between the British and American establishments followed, and much of the early work carried out in the Laboratory at Lulworth was confirmed by the American investigators. That the importance, in relation to the war effort, of the work of the Council's research team at Lulworth was widely recognised is shown by the acceptance of its recommendations by the Directorate of the Royal Armoured Corps and the Ministry of Supply, and by the choice of a member of the team to accompany War Office delegations to America to study American design of armoured vehicles and American Army policy regarding tank warfare.

The Royal Naval Personnel Research Committee

The Royal Naval Personnel Research Committee was appointed in November 1942 following a request from the Board of Admiralty for the establishment of a Committee with functions generally analogous to those of the Flying Personnel Research Committee and the Military Personnel Research Committee, but subserving naval interests. The Board suggested that it should be a Committee of the Medical Research Council, whose Secretary, Sir Edward Mellanby, should act as Chairman; and that the membership should include the Medical Director-General of the Navy and another naval Medical Officer, the Director of Scientific Research, Admiralty, and two Executive Officers, with the attendance of the Senior Psychologist as the occasion required. Dr. B. S. Platt, of the Council's staff, served as a further member on behalf of the Council and Dr. G. L. Brown, of their staff, was appointed Secretary. The membership of the Committee, which is given on p. 423, has remained substantially the same since its inception, but there have been certain additions. The principal representatives of the Executive Branch of the Royal Navy have been the Director of Tactical, Torpedo and Staff Duties Division of the Admiralty, together with the Director of Miscellaneous Weapons Development, who was later replaced by the Deputy Director of Naval Equipment, representing the Controller's interests. As the work of the Committee developed, it became

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necessary to add, as permanent members, a representative from the Staff of Admiral, Submarines and a Medical Officer to provide liaison with the Staff of Admiral, Air. In 1943 Surgeon Lieutenant-Commander F. P. Ellis, R.N., was appointed Naval Medical Secretary to assist in the organisation of the Committee's work. The U.S. Naval Medical Liaison Officer in London has attended meetings.

The first investigation undertaken by the Committee was into conditions in Coastal Force craft. Representatives visited coastal force bases and made a number of recommendations directed towards improvement in clothing and living conditions, particularly in regard to the reduction of condensation and the elimination of noise. As a result of the Committee's recommendations, the Medical Director-General appointed Surgeon Lieutenant-Commander H. E. Holling, R.N.V.R., to act as a special Medical Officer in the Directorate of Coastal Forces, Materiel, and to look after matters affecting the fighting efficiency of Coastal Force personnel.

The Committee's interest in the effects of climatic conditions was further exemplified at this stage by arrangements being made for Surgeon Captain M. Critchley, R.N.V.R., to make observations on conditions during passage on a northern convoy to Murmansk and Iceland. The success of this method of obtaining precise and impartial information from a medical observer led subsequently to further expeditions to study climatic effects, which will be referred to later.

Early in 1943, the Committee was confronted with a task of an entirely different nature. Developments were taking place in underwater warfare which led eventually to the extended use of the human torpedo and the X craft submarine, and to the use of divers on a large scale for reconnaissance, for clearance of beach obstructions, and for the recovery of enemy mines.

The Admiralty wished for a considerable extension of physiological research on diving and cognate matters, and asked the Committee to undertake its co-ordination. This led to the formation of the Sub-Committee on Underwater Physiology (p. 424), which contributed some of the most notable material with which the Committee was concerned. The part played by the National Institute for Medical Research in the work is described on pp. 207-9. In addition to this, a recommendation by the Sub-Committee led to the setting up of the R.N. Physiological Laboratory under the direction of Surgeon Commander C. L. G. Pratt, R.N.V.R. The Laboratory is situated in proximity to the submarine base at Fort Blockhouse and is still investigating problems of underwater physiology in the Royal Navy. The Sub-Committee was fortunate in having at its disposal the services of Professor J. B. S. Haldane, Commander W. O. Shelford, R.N., and Surgeon Lieutenant-Commander K. W. Donald, D.S.C., R.N., of the Admiralty Experimental Diving Unit. Three separate laboratories were thus involved in the difficult and dangerous studies of problems of diving, and the Committee sponsored a number of sea trials of diving gear, which also involved the Interservices Research Bureau, then developing such gear for other purposes. Although co-ordination of these various activities was on occasion difficult, the Sub-Committee was able to make substantial contributions to the operational effectiveness and safety of divers using self-contained gear.

A later development of the underwater studies was the work on diving equipment for use in tropical seas, to which reference is made in the report of the Neurological Research Unit at the National Hospital, Queen Square, London (p. 260).

In addition to its work on diving, the Sub-Committee fostered the development of air purifying gear for submarines and instituted instructional courses for submarines' commanding officers. Sea trials were carried out in H.M.

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Submarines under war conditions, and data on atmospheric conditions were collected. Trials based on more recent developments are continuing. The Sub-Committee has recently been able to advise the Admiralty Submarine Escape Committee on some of its physiological problems, and on the experimental work necessary to solve them.

In February 1943, the Committee, as a result of a request from the Director of Naval Ordnance for advice on means of promoting the efficiency of Director crews, set up a Gunnery Sub-Committee (p. 423). Its initial studies had the object of improving the conditions of work for men under exposed conditions in Director Control Towers, but it soon became obvious that the Sub-Committee could also be of assistance in regard to the general design of gunnery equipment of many types. In the case of Directors, clothing was a question of major importance, and the Gunnery Sub-Committee felt obliged to delegate its interest in this to another Sub-Committee (p. 423), set up specifically to study the design of clothing to meet particular Service requirements. A problem which has been, and remains a major interest of the Gunnery Sub-Committee is that of the seated operator working sights and hand-wheels, there being a natural tendency on the part of the designers to assemble components in a manner giving the maximum of constructional simplicity, which too often makes little allowance for the needs of the human operator. The Sub-Committee enlisted the help of Professor W. E. LeGros Clark and Dr. A. G. M. Weddell of the Department of Human Anatomy, Oxford, and their work in this field has been of the greatest value. They have been able *inter alia* to design seats which provide a secure, stable and comfortable posture for the operator, allow him to use optical instruments or hand-wheels without strain or contortion, and permit of comfortable relaxation during the periods of waiting. Although intended primarily for Directors, the seats are of general application and are coming into general use in the Service. Similar studies have since been extended to other aspects of gunnery, particularly to the design of tracking devices and sights; very valuable help on these questions has been given by workers in the Psychological Laboratory and the Applied Psychology Research Unit at Cambridge (pp. 134 and 319).

Another aspect of the problem of the human operator was met when measurements were made by Dr. J. A. B. Gray of the energy output of Turret crews. He found out that certain tasks required of the men in handing rooms and magazines demanded an energy output equal to or even greater than that of a trained athlete. With the inevitable speeding up of naval warfare it became apparent that restriction of the rate of fire depended on limitations not so much of the mechanical equipment as of the men who had to feed it. Re-design of equipment, and a re-allocation of tasks, have now done much to counteract this difficulty and, together with careful regulation of environmental temperature and humidity, will probably reduce the likelihood of human breakdown.

This question of the environmental conditions in gun-turrets has received much attention from the Committee, interest in it being further stimulated by reports from northern convoys of particularly severe conditions in gun-houses. Arrangements were made for Mr. M. G. Bennett and Mr. F. E. E. Smith to make observations and experiments in ships of the Home Fleet, and, as a result, recommendations were made and quickly implemented for the installation of thermal insulation in the gun-houses of several classes of H.M. ships. Although this measure was primarily designed to alleviate the condensation occurring in Arctic waters, it had an application also to ships in the Tropics, and, although admittedly a temporary expedient, it has effected improvement in gun-house conditions. Further development of insulating materials and methods is in progress.

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The realisation, in the Spring of 1943, that intensive naval operations in tropical waters were imminent impelled the Committee to recommend the dispatch of two observers, Surgeon Captain M. Critchley, R.N.V.R., and Surgeon Lieutenant-Commander H. E. Holling, R.N.V.R., to the Mediterranean, Levant and Eastern Fleet. These observers reported to the Committee early in May, 1944, their reports making it clear that the atmospheric conditions in H.M. ships were not conducive to a maintained high level of efficiency in their complement. At the same time, the Admiralty asked the Committee to undertake research work with a view to determining standards of habitability in ships which would be consistent with maximal efficiency. This request led to the formation of the Habitability Sub-Committee (p. 423), which initiated investigations on a considerable scale. It was clearly necessary, in the first place, to secure quantitative data on the environmental conditions in H.M. ships under wartime conditions, with the additional handicaps imposed by the necessity of darkening ship, of swollen complements and of rigorous damage control measures, all of which affect adversely the air conditions on board. With this end in view, the Committee dispatched to the Eastern Fleet a mission consisting of Surgeon Lieutenant-Commander F. P. Ellis, R.N., Surgeon Lieutenant-Commander H. E. Holling, R.N.V.R., and Constructor Lieutenant-Commander Brokensha, R.C.N.C., with technical assistants and the necessary apparatus. The collaboration of a naval constructor with medical men proved exceptionally valuable, and the mission, in addition to producing unique data on conditions in the Fleet, were able to recommend material improvements in the living conditions in most of the ships which they visited.

Simultaneously with the dispatch of the mission, steps were taken to start laboratory investigations in this country, and the Admiralty equipped two climatic chambers in the National Hospital for Nervous Diseases, London, and one in the Department of Psychology at Cambridge. In the laboratories, physiological and psychological studies, respectively, were made of the effects of hot and humid environments on naval ratings doing tasks similar to those encountered in ships cruising and in action. More detailed reference to some of these investigations is made on p. 258. It became clear, early in the progress of the work, that the levels of temperature, humidity and air movement, suggested by the Sub-Committee as the limits permissible on *a priori* grounds, were in fact very near the figures at which fighting efficiency would suffer, and the observations of the Eastern Fleet mission made it clear that such temperatures were frequently exceeded in living compartments and compartments in which the work done was vital to the ship's fighting organisation. Steps were immediately taken by the Admiralty to improve this state of affairs, in the first place, by temporary expedients and, secondly, by making alterations in the design of ships under construction and planned. In this connection, a handbook on environmental warmth and its measurement, prepared by Dr. T. Bedford (p. 317) for the Royal Naval Personnel Research Committee, was issued by the Council as *M.R.C. War Memorandum No.* 17; published with it was a series of large-scale charts for making the necessary calculations. The handbook and charts have been adopted by the Admiralty for use in H.M. ships, and they should have many applications also to problems of industrial hygiene.

Although the laboratory work in this country was of immediate value and gave most interesting pointers towards future developments, it clearly was not ideal to apply directly to men living in the tropics, the results of work done only under the artificial conditions of the laboratory in a temperate climate, and a planning mission, consisting of Professor H. C. Bazett and Surgeon Captain Critchley, R.N.V.R., was accordingly dispatched to the Far East to organise a Tropical Research Unit in a suitable locality; Professor Bazett is

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a British subject who holds the Chair of Physiology in the University of Pennsylvania; he has great experience of climatic physiology, and the Council were fortunate in being able to enlist his help. At the time of the mission, Bombay showed the most promise of providing a shore base with the necessary facilities and the all-important access to Naval ratings as volunteer subjects for experimental work. Laboratories were chosen, and equipment assembled in this country and sent to India. Soon afterwards, however, the strategic situation in the Far East necessitated the formation of the British Pacific Fleet, with a great reduction of the number of ships based on Ceylon and using Indian ports, so that the likelihood of Bombay being able to provide access to ships and a supply of subjects became remote. The Bombay scheme was, therefore, abandoned, and the possibility of transferring the Unit to Singapore was considered. The capitulation of Japan made this feasible, and Surgeon Captain S. G. Rainsford, R.N., joined the staff of S.A.C.S.E.A. (Supreme Allied Command, South East Asia), with a view to starting the laboratory in Singapore.

Preliminary arrangements have now been made with the King Edward VII Medical College, Singapore, and the Colonial Office, for the establishment of a Research Unit for the study of climatology in the building of the College; and research staff appointed by the Council and the Medical Department of the Navy are ready to start work as soon as the plans have been implemented.

An integral part of the Climatological Research Unit, as originally planned, was a seagoing component which would be able to continue the work of the Habitability mission in making physiological observations in ships under active service conditions in tropical waters. Arrangements were, therefore, made for Surgeon Lieutenant J. A. B. Gray and two technicians to proceed in H.M.S. *Pioneer,* which was intended to be in part a research ship, to join the Fleet Train of the British Pacific Fleet. The favourable course of the Eastern War, however, affected adversely the physiological work, since ships were relatively seldom in the action state, and most operations took place in temperate or subtropical waters. Surgeon Lieutenant Gray was able, nevertheless, to make valuable observations on the causes of excessive heat in ship's compartments, and to undertake a limited amount of more purely physiological work.

The work of the Habitability Sub-Committee has been extended to submarines, and Surgeon Lieutenant-Commander Ellis has completed a survey of conditions in one of H.M. Submarines in arctic and in tropical areas, under conditions approximating to those of a war patrol. Some preliminary observations have also been made on the bacterial content of the air of ships —a problem of major importance in connexion with the spread of epidemics, and the possible use of bacterial agents in warfare; an account of this work is being published by the Council as part of a *Special Report* dealing with problems of air hygiene.

Finally, the Sub-Committee has been requested by Admiral (Air) to investigate living and working conditions in shore establishments, and has been able to utilise, for the benefit of the Service, the long experience of workers for the Council's Industrial Health Research Board in solving kindred problems in industry.

Reference has already been made to the formation of a Clothing Sub-Committee, which was needed primarily to consider the requirements of Gunnery ratings in exposed positions. This Sub-Committee worked under the inevitable handicap of the shortage of supplies in this country during wartime, and its programme was restricted to a certain extent by lack of sufficient numbers of trained observers to carry out effective field trials. Nevertheless, it did very important work. There is, of course, a close relationship between a man's clothing and his tolerance of climatic extremes, and the Clothing

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Sub-Committee maintained close association with the Habitability Sub-Committee in regard to such problems as the optimal clothing for ratings manning the lower quarters of turrets. It was able to design and test anti-flash gear which was capable of providing adequate protection without imposing too great a load on the wearer's heat regulation, and, in devising suitable action rig for tropical wear, it had the benefit both of the experience of Dr. R. B. Bourdillon and his colleagues in their studies of methods of protection against flame (pp. 45, 136 and 209), and that of the workers at the National Hospital and elsewhere who had investigated problems of tropical equipment for the Army.

The Sub-Committee also examined questions of suitable clothing for service in the arctic, and sent an observer, Mr. J. C. D. Hutchinson, to the very elaborate Cold Weather Clothing Trials carried out in Canada by the Dominion Armed Forces. Canadian cold weather clothing, and electrically heated clothing, are under trial in the Royal Navy at the present time.

The interests and activities of the Sub-Committee extended further to the problem of blast-protection for gunners, and to the design and testing of body armour and flotation devices for Coastal Forces and other branches of the Service.

The brief account given above summarises only the major activities of the Royal Naval Personnel Research Committee and its Sub-Committees; it omits many items, less important in respect of the results achieved, in which the Committee and its Sub-Committees have been involved. In the early days of the Committee's work, auditory problems, particularly as regards anti-submarine listening, bulked largely in the agenda, and the Committee sponsored studies on selection of personnel and on the training of operators. Problems of a more purely physiological nature were inevitably presented, but the shortage of men suitably trained for this type of work, and the pressure of more urgent problems, often made it impossible to explore these under war conditions.

Questions of selection and training have also been studied by the Visual Problems Sub-Committee (p. 424), and recommendations relating particularly to the testing of colour vision and vision at night have been made.

In conclusion it may be stated that the work of the Committee is continuing, at the request of the Board of Admiralty, though on a much reduced scale. Its future is largely bound up with the development of medical research by the Royal Navy itself, since members of the staff of the Council can no longer devote their whole time to service problems, and are obliged to revert to an advisory capacity. When the projected Royal Naval medical research organization has come into being, the main Committee, and its Sub-Committees, will still be able to perform a useful function as co-ordinators of activity within the Service, and as a link between it and institutions doing more academic work. The fact needs little emphasis that a Committee of this sort exists as a useful body only so long as it has at its disposal a sufficient number of competent investigators to solve its problems.

It is appropriate at this point to recognise how much the Committee owes for its achievements to Surgeon Vice-Admiral Sir Sheldon Dudley, late Medical Director-General of the Navy, with whom and with whose staff the most friendly and mutually helpful relations have been maintained; similar close and satisfactory relations are continuing between the Committee and his successor, Surgeon Vice-Admiral H. St. C. Colson.

The effectiveness of the Committee in those of its activities which were largely divorced from orthodox medicine has been due to the vision and enthusiasm of the many executive officers who appreciated its value to the Service, and have been the most helpful and zealous collaborators in its programme.

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VII

HEALTH RESEARCH IN INDUSTRY

Research on problems of the health and well-being of workers in industry has always formed a substantial part of the Council's programme, and many fruitful investigations in this field had been sponsored by the Industrial Health Research Board (p. 428) and by special Committees of the Council before the war. It is of interest to recall that the Board, which since 1920 has been part of the Council's organisation, developed originally from the Health of Munition Workers Committee, set up in 1915 to examine questions of hours of work in relation to health and efficiency which were very similar to some of those arising during the recent conflict. In the interval between the two wars a mass of accurate scientific data on problems of industrial physiology and psychology had accumulated, very largely as the result of studies made by workers for the Board. Accounts of most of these investigations had been published in monograph form, in the well-known series of " pink reports " of the Board, issued by the Council, and many of the recommendations had been implemented by progressive employers, with good effect upon the health and efficiency of their staffs. Since, however, it seemed likely that some of the lessons learnt might be forgotten under the stresses of an unprecedented munitions " drive " for the second world war, a summary of the chief research findings " capable of immediate application in furtherance of the National Effort " was published early in 1940, under the title of " Industrial Health in War " (*Industrial Health Research Board Emergency Report* No. 1); subsequently, four other *Emergency Reports* dealing with the results of both pre-war and new researches on human factors influencing industrial output were published, as also were five " pink reports " of the Board on new studies made between 1939 and 1945, and a series of popular pamphlets intended to bring home the lessons of research on industrial health and efficiency to a wider public than would normally be reached by the more technical reports; further reference to the Council's war-time publications on problems of industrial health is made on p. 200.

The fear that the lessons learnt in 1915-17, regarding the deleterious effects of excessively long hours of work on health and output, might be forgotten under the stress of a new and even fiercer struggle for national survival proved to be well-founded—as was shown by what happened in industry in the months following the evacuation from Dunkirk. At that time the call was for more and more munitions to replace those lost upon the Continent, and to prepare for the next stage of the conflict. The response of industry was commensurate with the urgency of the situation, and for many weeks both men and women in war factories voluntarily endured excessively long working hours without holidays. The result, as might be expected, was that although initially there was an exceptionally high level of output, it could not be maintained, and the ill-effects of the almost superhuman effort voluntarily endured were soon reflected in an increased amount of sickness absence. These facts were clearly established in a series of surveys made by workers for the Board, of which the results were published in a pamphlet entitled " Hours of Work, Lost Time and Labour Wastage " (*Industrial Health Research Board Emergency Report* No. 2): in this it was recommended that " over an extended period, the weekly hours of work should generally not exceed 60 to 65 for men and 55 to 60 for women "; the study also, like its predecessor made by the Health of Munition Workers Committee, stressed the importance of the week-end rest-break, and it further showed the value of the newly-introduced system of staggered holidays. The lower figures for weekly working hours suggested

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in that publication were subsequently accepted by Government as the maxima compatible with continued health and working efficiency, and sustained output over a long period.

The programme sponsored by the Board itself from its inception until 1939 had related chiefly to the physiological, psychological and environmental factors affecting the healthy worker in industry, and the peculiar features of the industrial situation of the recent war—including the need to employ vast numbers of women, of inexperienced new workers and of workers from the older age-groups—presented a large number of urgent and difficult problems, which were studied on similar lines. Two new and very important developments in industrial health research during the war years must, moreover, be mentioned here. The first was the widespread application of methods of research in industrial physiology and psychology to the personnel problems of the Fighting Services, and conversely the finding that the results of many researches carried out initially for one or other of the Services had far-reaching practical applications also to industry; examples of both kinds have been given in the section of this Report dealing with " Personnel Research " above. Reference has been made there to the extensive programme of research for the Flying Personnel Research Committee of the Air Ministry, carried out at Cambridge by a team of workers under Professor F. C. Bartlett's direction, which was constituted by the Council in 1944 into a Research Unit in Applied Psychology; it has also been mentioned that certain other members of the Council's staff, who had previously been engaged on industrial studies for the Board, worked mainly or partly for the Service departments or the Personnel Research Committees during the period of hostilities, their special experience of applied psychology or environmental physiology lending itself equally to studies of the human factor in industry or of the reactions of the sailor, soldier and airman to the stresses and exigencies of total war.

The second major development in regard to industrial health research in the war years, was a substantial increase in the Council's programme of work on occupational hazards and diseases, with a corresponding widening of the original terms of reference of the Board. Various problems of this nature—such as lung disease in coalminers and cotton spinners, miners' nystagmus, and the toxicity of industrial solvents—had been the subjects of special studies directed by expert Committees appointed by the Council before the war, but the war itself brought a further train of kindred or different problems demanding urgent attention. Among the earlier consequences of this were: the appointment in 1942 of Professor A. W. M. Ellis as the Council's whole-time Director of Research in Industrial Medicine, a post which he held until he became Regius Professor of Physic in the University of Oxford later in the same year; the establishment by the Council, in 1943, of a new Department for Research in Industrial Medicine at the London Hospital, which, under the direction of Dr. Donald Hunter, has already carried out a very wide programme of research in industrial disease and toxicology, as indicated on pp. 313-316; and the setting up of Units for research on wound infection (p. 266), burns and scalds (p. 270) and traumatic " shock " (pp. 53 and 54)—all problems with an important bearing on industrial injuries—at Birmingham, Glasgow and Birmingham, and Newcastle and Sheffield, respectively. Later developments, towards the end of the period covered by this Report, included the formation by the Council, in association with the Ministry of Fuel and Power, of a Pneumokoniosis Research Unit at Cardiff, under the direction of Dr. C. M. Fletcher, to extend the earlier work on lung diseases in coalminers which is summarised below, and to study questions of rehabilitation for the men affected; the reconstitution of the Wound Infection Research Unit at Birmingham (p. 266) into a Research Unit in Industrial Medicine, with special reference to skin diseases, under the direction of Dr. J. R. Squire;

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and the organisation, at the request of the Ministry of Works, of an inquiry into physiological and psychological problems in the building industry, which is being directed by Professor C. A. Mace, in relation to the national re-housing programme.

At the outbreak of war Professor E. P. Cathcart was Chairman of the Council's Industrial Health Research Board; he was succeeded in 1940 by Sir Wilson Jameson. When the Board was reconstituted in 1942, Earl De La Warr became Chairman, being later succeeded by Professor Bartlett. Air Vice-Marshal Sir David Munro, who had been Secretary of the Board since 1930, resigned in 1940 to take up the appointment of Chief Medical Officer to the Ministry of Supply. The Council are glad to place on record their high appreciation of Sir David Munro's services while a member of their staff; his extensive practical experience of many different branches of medical work rendered his advice and help of special value to the Council in regard not only to the work of the Board but to numerous other aspects of their research programme. For the remainder of the war period, Dr. R. S. F. Schilling, seconded from the Factory Department of the Ministry of Labour and National Service, was the Secretary of the Board, and latterly he had the assistance of Dr. Joan M. Faulkner.

In August, 1944, Dr. May Smith, who had been an investigator for the Board from its earliest days, retired from the Council's service. Her important contributions to the science of industrial psychology were officially recognised by the award of the O.B.E.

Environmental Factors in Industry

Ventilation and air hygiene.—The ventilation of air-raid shelters, of factories and other buildings under war conditions, presented urgent problems which were often accentuated by the requirements of the " black-out "; particular difficulties of ventilation and air hygiene arose in factories where noxious fumes or dusts were liable to accumulate. Following requests from the Government departments concerned, these problems were studied early in the war by Dr. T. Bedford and other members of the Council's staff at the London School of Hygiene (p. 317). Their recommendations led to the introduction of improved methods of ventilation and of dealing with poisonous materials, such as T.N.T., which reduced the risks to health. Closely related to these studies of ventilation problems was the work on airborne infection and air purification, carried out as an important part of the war-time research programme of the National Institute for Medical Research (p. 213).

Industrial lighting.—The problems of natural and artificial lighting of factories and offices under war conditions, including conditions of " black-out ", were intensively studied by Mr. H. C. Weston of the Council's staff. His work in this field, on behalf of the Departmental Committee on Lighting in Factories and other official bodies, is discussed on p. 318. These investigations had a direct bearing on the drafting of the Factories (Standards of Lighting) Regulations, 1941.

Artificial sunlight.—Artificial sunlight treatment (ultra-violet light irradiation) has certain established uses in medicine, but the claims often made for its supposed effect as a general " tonic ", and preventive of colds and other illnesses, have rested on much less secure foundations. On the assumption that it should have such an effect, and perhaps compensate to some extent for the more objectionable features of the " black-out " and other wartime working conditions, an increasing number of industrial undertakings began during the war to introduce solaria for the regular treatment of their employees by exposure to the rays of quartz mercury arc lamps

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for short periods weekly. It thus became a matter of practical as well as scientific importance to examine whether such treatment really had the beneficial effects attributed to it. A carefully controlled investigation with this object was carried out in 1944-45 by Dr. Dora Colebrook and others, under the guidance of an *ad hoc* committee of the Industrial Health Research Board. The observations were made on more than 3,000 volunteers—in a Government office, a factory and a coal-mine—and the findings were statistically assessed (p. 328). The results were disappointing in that they provided no evidence that the treatment was of benefit in lessening sickness absence, or in reducing the severity of colds and other ailments. Even as regards subjective or " psychological " benefit from the treatment the opinions of the volunteers were by no means unanimous. A full account of the investigation has been published as *Industrial Health Research Board Report* No. 89.

Industrial Psychology

Hours of work, absenteeism and cognate problems.—Before the war, Dr. S. Wyatt and his colleagues, working for the Industrial Health Research Board at Manchester, had carried out a large number of field investigations of the reactions of industrial workers to the nature and conditions of their tasks, with particular reference to the effects of fatigue, boredom and incentives on health and output. The war provided both the need and the opportunity for further studies of a similar kind, especially as regards hours of work, the principal causes of absence from work, and the effects of night work. An account of these investigations, with the names of those who took part in them, is given on p. 324, but it is appropriate to mention here that the publication " Hours of Work, Lost Time and Labour Wastage ", referred to above, and the important practical recommendations resulting from it, were based on studies made in 1940-41 by Dr. Wyatt and his team.

Fatigue.—In relation primarily to Service needs, a series of experimental studies of the factors, beyond mere duration of time, that are involved in the development of fatigue after skilled work was made in the Psychological Laboratory and the Research Unit for Applied Psychology at Cambridge. These investigations are discussed briefly on p. 322; though undertaken with specific regard to problems referred by the Flying Personnel Research Committee (p. 132), they have obvious significance also for industry.

Selection and training.—The use of psychological methods in personnel selection both for the Services and for industry has already received wide publicity. In developing tests for the purpose, and in assessing their validity, Mr. E. Farmer, Mr. E. G. Chambers and other workers for the Industrial Health Research Board at Cambridge have had an important share. Both before and after the outbreak of war Mr. Farmer and a number of his colleagues were engaged in organising selection tests for recruits for various branches and duties of military service, until, in 1941, this type of work was held to have passed the " experimental " stage and to be ready for systematic application on a wide scale through a special Directorate of the War Office (p. 321). Although much of the research on selection done for the Forces is hardly less applicable to industry, special investigations, with which Dr. Alice Heim, of the Cambridge Unit, was largely concerned, were made at Ministry of Labour Training Centres and in certain war factories (p. 321). In addition to intelligence tests, various others, such as " inspection tests ", " manual dexterity tests " and " alignment tests " were used for assessing specific aptitudes; a series of tests was also prepared to help in job selection for the blind.

Accidents.—Much work on the problem of preventing industrial accidents —particularly by identifying the " accident prone " and excluding them

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from dangerous tasks—had been done by Mr. Farmer and his colleagues before the war. A summary of the results of these studies, together with an account of some of the environmental and other factors predisposing industrial workers to accident, was published in 1942 under the title of "The Personal Factor in Accidents" (*Industrial Health Research Board Emergency Report* No. 3). A brief account of the work on accident prevention carried out during the war by members of the staff in the Applied Psychology Unit at Cambridge is given on pp. 322-3.

Design of display panels and controls for precision instruments.—Work undertaken in the Cambridge Unit for the Flying Personnel Research Committee (p. 133), under the inspiration and leadership of the late Dr. K. J. W. Craik, has led to improved methods of "display" and "control" for precision instruments; their reading has been made more accurate and quicker, and their adjustment easier. Improvements such as these not only increase working efficiency, but also diminish fatigue and strain for the operator.

Neurosis in industry.—The Industrial Health Research Board organised a wartime inquiry into the incidence of neurosis among factory operatives in the engineering industry. Dr. Russell Fraser directed a group of investigators centred on Birmingham, and later a second group was formed under Dr. Elizabeth Bunbury, which carried out parallel studies in London. The names of the principal investigators are listed on p. 342. Altogether some 3,000 men and women, representing a random sample of over 30,000 workers from 13 light or medium engineering factories, were interviewed and examined. The main findings were that, during the six-months period covered by the survey, 10 per cent. of the workers had suffered from disabling neurosis and a further 20 per cent. from minor forms of neurosis; neurosis was responsible for between a fifth and a quarter of all absences from work. Of a large number of possible determining factors whose importance was assessed, certain features in the individual's constitutional make-up and environmental experience were shown to correlate closely with a high incidence of neurosis. A full account of the investigation has been published as *Industrial Health Research Board Report* No. 90.

Industrial Diseases and Toxicology

Diseases due to inhaled dusts

Lung disease in coalminers.—In 1937, at the request of the Home Office and the Mines Department, the Council organised a large-scale investigation into the incidence, causes and prevention of lung disease due to dust in the South Wales coalmines. The researches, which included clinical, radiological, pathological, physical, geological and chemical studies, were directed and co-ordinated by a special Committee on Industrial Pulmonary Disease (p. 429), of which Professor C. G. Douglas was Chairman and Dr. E. L. Middleton, Secretary. The problem was urgent, since the numbers of miners certified as suffering from silicosis had been increasing yearly, particularly in the anthracite area; moreover it was believed locally that other disabling pulmonary conditions besides those recognised as "silicosis" were being caused by mine dust. The results of the investigations directed by the Committee were published in 1942, 1943 and 1945, in the Council's *Special Report Series* Nos. 243, 244 and 250. The medical survey showed that pulmonary abnormalities extended throughout this coalfield, but that the incidence and severity were highest in long-term anthracite colliers. A relationship was established between the incidence of pulmonary abnormality among the colliers (as judged by X-ray evidence) and the rank of the coal mined at

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the different collieries, though within the anthracite area there were also local variations in incidence. Furthermore, the medical survey and pathological studies confirmed the local belief in a disability other than true "silicosis", by bringing to light and defining another widespread form of pulmonary disease due to dust inhalation, which has been termed "dust-reticulation". The environmental survey and experimental studies confirmed that the primary factor responsible for the various pulmonary abnormalities was the air-borne dust, and analysed this factor further; they provided information on the strata most likely to be the source of danger, and on the contributory responsibilities of atmospheric conditions in the mines, and of methods of working. These studies suggested that differences between the hazards in the different mines were a function both of the quantity of the dust and of its physical and chemical nature. Current opinion in the U.S.A. tended to view the concentration of air-borne quartz as the prime determinant of the incidence of pulmonary disease: the investigations in South Wales, while likewise incriminating quartz, suggested that other constituents of the dust (both coals and other minerals) might also be of decisive importance through enhancing, reducing or modifying the noxious action of the quartz. The practical results of these investigations have so far been of interim character, yet they have been substantial. Thus, legislation was subsequently provided to broaden the compensation coverage of all coalminers, so as to include, under the title "Pneumokoniosis of Coalminers", dust-reticulation as well as the pulmonary abnormalities previously recognised. Powers were also taken to enable various new methods of dust suppression, which had been devised by South Wales engineers and scientific workers during the progress of the Council's inquiry, to be compulsorily introduced where deemed necessary. These methods include water-infusion of the coal face before working it, and sprays used in connection with mechanical coal-cutters.

Many fundamental questions remain unanswered, and the problem of preventing pneumokoniosis in coalworkers is only partly solved; meanwhile, the loss to the industry of men with the disease continues, with its consequent deterrent effect on recruitment. At the request of the Ministry of Fuel and Power and with its co-operation, the Council have accordingly proceeded to a second stage of inquiry, by forming in 1945 a special Pneumokoniosis Research Unit in Cardiff under the direction of Dr. C. M. Fletcher, as mentioned on p. 154. The work of the Unit began after the end of the period under review, and will be discussed in the next Report.

Other dust diseases.—Various studies of the dust hazard in industries other than coalmining have been made by workers in the Department for Research in Industrial Medicine at the London Hospital, and are noticed on p. 313, below. They have included investigations into the incidence of lung disease among iron and steel foundry workers, and among workers in certain other occupations; observations on the effects of aluminium dusts, and their possible value for the treatment of silicosis in tin-miners; and clinical studies of acute pneumonias following the inhalation of bagasse (dried sugar-cane fibre) dust.

Dust-sampling instruments.—In relation to the work on the risks of dust inhalation in coalmining and other occupations, comparative tests of different dust-sampling instruments have been undertaken by Mr. C. N. Davies as a member of Dr. Bedford's team at the London School of Hygiene (p. 317).

Industrial Toxicology

The requirements and conditions of industrial work in wartime raised many problems of toxicology. The manufacture of certain explosives and other substances used for military purposes carries known risks of industrial poisoning, which were sometimes accentuated by environmental circumstances

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directly connected with the war; for example, as mentioned on p. 155, the need for a strict " black-out " often made proper factory ventilation difficult. Moreover, during the war period, many materials which were new to industry were used on a large scale, before their possible effects on health had been explored.

Much research on known and potential health hazards due to toxic agents was carried out by workers for the Council in the war years. The numerous studies of this nature made by the Department for Research in Industrial Medicine at the London Hospital are summarised on pp. ; some of these have related to hazards only recently recognised, such as that of fluorosis due to the use of fluorides in aluminium factories. Other investigations deserving mention include the inquiry into the early manifestations of T.N.T. poisoning among workers in filling factories, organised in 1942 by Professor L. J. Witts and Professor A. W. M. Ellis, with the co-operation of Dr. Alice Stewart and a group of medical student volunteers; the dangers of poisoning by carbon tetrachloride, trichlorethylene and other substances used in industry have also been examined by Professor Witts and his colleagues. The part played by the Department for Research in Industrial Medicine in supervising the health of workers with uranium is mentioned on p. 314; another aspect of the risks of working with radioactive materials, namely the degree to which such substances may be absorbed into the body during the process of luminising, was examined for the Council by Professor S. Russ and co-workers (p. 343).

Effects of Vibrating Drills and Other Tools

A study of the effects produced by the vibrations of pneumatic drills and similar appliances on the hands of the operators is being made in the Department for Research in Industrial Medicine at the London Hospital (p. 315). The prolonged use of such appliances as mechanical road-drills has been shown to cause certain circulatory changes in the hands. The objects of the research are not only to determine the nature and results of these effects, but also to analyse the physical character of the vibrations causing them, with a view to indicating where risks may be lessened by appropriate modifications of tool design.

Other Health Investigations in relation to Industry

At the request of the Ministry of Labour and National Service, a controlled test of the value of short-wave therapy for the treatment of the common cold was arranged by the Council early in the war. The results indicated that any symptomatic relief produced by such treatment was insufficient to be of practical value. Later, the Council appointed a special committee (p. 427) to organise clinical trials, in industrial workers and others, of the antibiotic " patulin " in the treatment of the common cold. The results, reported in the *Lancet* (1944, **ii**, 373), failed to confirm the hopes for this treatment which had been raised in earlier tests on a smaller scale.

Health Records in Industry

For the satisfactory study of trends of sickness in industry—whether within a particular factory, from factory to factory or from trade to trade—it is important to have an efficient, generally accepted method of recording sickness absence. The method must be relatively simple, and be equally applicable to large or small factories. A special committee of the Industrial Health Research Board, under the chairmanship of Dr. A. J. Amor, then Chief Medical Officer, Ministry of Supply, was appointed to recommend the best means of keeping such records. A preliminary report of this committee's findings was published in 1944 as *Industrial Health Research Board Report* No. 85.

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Rehabilitation Problems in Industry

Among the aspects of industrial health research which have received increasing notice in recent years is that dealing with the rehabilitation of workers suffering from occupational or other disabilities, and their subsequent placement in occupations compatible with their powers. Work on these lines is being carried out as part of the programme of the Department for Research in Industrial Medicine at the London Hospital (p. 315); particular attention has so far been given by this group to the satisfactory placement in industry of patients with chronic heart disease. Studies in the rehabilitation, and placing in alternative occupations, of coalminers disabled by pneumokoniosis are being undertaken on an extensive scale by the Pneumokoniosis Research Unit (p. 158) in South Wales. Research on rehabilitation problems by workers in the Applied Psychology Unit at Cambridge is mentioned on p. 323.

Conference on Industrial Health Research

A conference to discuss current problems of industrial health research was organised by the Council's Industrial Health Research Board at the London School of Hygiene and Tropical Medicine in September, 1944. It was attended by representatives of Government Departments, of Management and of the Trade Unions, as well as by many industrial medical officers and medical research workers. The Chair at the various sessions was taken in turn by Sir Edward Mellanby, by Dr. E. R. A. Merewether (H.M. Senior Medical Inspector of Factories), by Mr. J. L. Smyth (then Secretary of the Social Insurance Department of the Trades Union Congress) and by Professor F. C. Bartlett. A report of the proceedings, giving the principal communications in full, was published in pamphlet form under the title "Health Research in Industry" (H.M. Stationery Office, London, 1945).

VIII

SPECIAL EMERGENCY SERVICES

During the war and in the period immediately preceding it, the Council were called upon to assist the Government not only in the promotion of special types of research but also in the administration of certain emergency services of a highly technical nature. Apart from much help of this kind given on particular occasions, the programme under this heading consisted of four regular items of widely varying magnitude, three of which had a common origin.

As long ago as 1934 the Secretary of the Council was consulted by the Government about the possible dangers of bacteriological warfare, if such methods should be used against this country by an enemy, and two reports drawn up by experts acting on the Council's behalf were submitted. In 1937 the Council were invited to take part in a closer consideration of the defensive measures which ought to be taken, and subsequently they were entrusted with executive responsibility for some of the measures decided upon. In the first place, it was considered necessary to build up reserves (and production potential) of various vaccines and antitoxins which might be required for combating outbreaks of infectious disease, possibly of kinds not ordinarily occurring; in the event, however, the larger part of this problem was concerned with the supply of antitoxins for use not as a defence against bacteriological warfare but for the more ordinary medical purposes of preventing tetanus and gas gangrene in the wounded and in air-raid casualties. In the second place, it was considered that this country was inadequately provided with laboratory facilities for the diagnosis and investigation of

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infectious disease, and that a special laboratory service should therefore be organised to make good this deficiency in the national defences; in this case also, bacteriological warfare was not the only danger in view, as there was at least as great a risk of natural epidemics occurring on a large scale as a result of possible mass movements of population and the partial breakdown of normal sanitary services. In the third place, it became clear that for this and other purposes there would, in the event of war, be an exceptionally heavy demand for trained pathologists and skilled laboratory technicians, so that special steps were necessary for the registration and direction of these categories of technical manpower.

The fourth item was of a different nature, relating to the need for the supply of human blood on a large scale for transfusion in the treatment of casualties, both in the Forces and among the civilian population. The Council's executive responsibility in this matter was originally limited to the organisation of supplies of stored blood for the resuscitation of air-raid casualties in the Greater London area. They were, however, also able to give considerable assistance to the Services, and to co-operate with the civilian organisation subsequently set up to cover the rest of the country. As the war went on the Council further became responsible for developments made possible by the introduction of technical processes for preserving blood plasma and serum in dried form.

The cost of the emergency services outlined above, and described in greater detail in the rest of this section, was not a charge upon the research funds at the Council's disposal but was separately provided through the votes of appropriate Government Departments. After the outbreak of war, the formula adopted was that these services were conducted on an agency basis on behalf of the Ministry of Health. There was, nevertheless, a complete delegation of executive responsibility, under which both the preliminary planning and the subsequent administration rested with the Council.

A paramount element in the Council's conduct of these technical affairs was scientific control from the centre. This task devolved largely upon one of their members, the late Dr. W. W. C. Topley, who devoted much thought and labour to the task of planning and, on the outbreak of war, was attached to the Council's headquarters office in a whole-time capacity as chief adviser in pathology. On his transference in 1941 to the Agricultural Research Council, as Secretary of that body, the work was divided. Professor G. S. Wilson, who had just succeeded the late Dr. W. M. Scott as Director of the Emergency Public Health Laboratory Service, became principal adviser in that regard. Dr. A. N. Drury, a member of the Council's scientific staff working at Cambridge, came to headquarters to deal with questions of blood supply and other matters; on his appointment in 1943 as Director of the Lister Institute of Preventive Medicine, he was in turn succeeded by Dr. D. P. Cuthbertson, borrowed from the University of Glasgow. Dr. (now Sir Philip) Panton of the Ministry of Health took Dr. Topley's place as chairman of the committee advising the Council about the emergency allocation of pathologists and technicians. Dr. (now Sir Percival) Hartley, of the Council's staff at the National Institute for Medical Research, continued to advise on the provision of serological supplies.

There was in addition a large amount of more strictly administrative work relating to these services, and this fell upon the regular members of the Council's staff—particularly upon Dr. A. Landsborough Thomson (assisted by Miss N. E. Bradshaw), with participation by the late Dr. D. K. M. Chalmers in respect of the blood supply depots until he joined the R.A.M.C. in 1943, and by Dr. F. J. C. Herrald in respect of immunological supplies.

The following accounts of the several services include summaries of the research activities undertaken by or in relation to two of them.

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Emergency Immunological Supplies

In 1937 the Council were entrusted by H.M. Government with responsibility for the co-ordination of supplies of certain serological products of special importance in wartime: brief reference to the measures taken by the Council to this end before the war was made in the Annual Reports for 1937-38 and 1938-39. The original object had been provision against possible bacteriological warfare or sabotage, but actually the largest task was the supply of great quantities of antitoxins to protect the injured against infections due to the contamination of wounds with soil and other material containing spores of the tetanus bacillus or of organisms of the gas-gangrene group. At a later stage the question arose of protection against louse-borne typhus and, in the Far East, against mite-borne scrub-typhus. Apart from needs arising specially from the war, the Council also had eventually to deal with supplies of materials for prophylaxis against diphtheria and, on a smaller scale, against measles.

At the outset, the Council had to make plans for the provision of supplies of tetanus antitoxin to meet the mobilisation requirements of the Fighting Services and the anticipated needs of the civilian population. This involved the production of antitoxin, both for the prevention and treatment of tetanus, on a scale out of all proportion to normal peacetime demands, and it entailed many technical difficulties. After careful consideration, it was decided that in all the circumstances the needs of a pressing situation could best be met in the first instance by supplying most of the antitoxin required for prophylaxis in the form of "natural" serum. The adoption of this policy not only made it possible to reach the target set with the least possible delay, but also resulted in important economies in materials and expenditure.

The decision was taken with full knowledge of the theoretical disadvantages of natural serum as compared with the refined and concentrated product, particularly in regard to keeping properties and liability to produce serum reactions. In the event, however, few reports were received of serum reactions after injections of natural serum. Allowance for decline in potency of the serum was made by stipulating that when issued it should contain an excess of antitoxin units, and at a later stage by increasing the volume of the dose in the case of the older preparations, on the basis of laboratory tests on samples stored under different conditions.

Supplementary stocks of refined and concentrated antitoxin for prophylactic use were also provided, however, so as to make the best use of existing manufacturing facilities in the country and to ensure that alternative sources of supply would be available in case of need. All the antitoxin for therapeutic purposes, for which there was a much smaller demand, was supplied in this form.

Arrangements for the provision of large stocks of polyvalent gas-gangrene antitoxin were likewise made, and in this case the technical problems were in some respects more difficult to solve. Opinion was divided as to the value of gas-gangrene antitoxin, particularly for prophylaxis, but the material had nevertheless to be supplied in a form suitable either for prophylaxis or for treatment, and the composition and appropriate dosage decided empirically in the absence of precise knowledge on these points. On the recommendation of the Anaerobes Sub-Committee of the War Wounds Committee (p. 30), the dosage was later increased and the relative proportions of the components altered. These modifications necessitated a very considerable new expansion of production, the more so in view of the steadily increasing use of the antitoxin for prophylaxis.

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As a result of the preparatory measures described above, adequate initial stocks of tetanus and gas-gangrene antitoxins were available for distribution to the Services and civilian Departments before the outbreak of war.

The Council had meanwhile made further arrangements with the manufacturers for continued production of the antitoxins on a wartime scale, and large reserves were accumulated and held in a common pool on which all Departments drew as required. Detailed distribution was in the hands of the respective Departments, but the Council were in a position to co-ordinate and anticipate the varying demands from all quarters. This scheme remained in operation until 1943, when responsibility for the supply of the materials was transferred to the Ministry of Supply. Up to the date of the transfer, the Council distributed from the pool approximately 4,500,000 prophylactic doses and 118,000 therapeutic doses of tetanus antitoxin, and over 380,000 bottles of polyvalent gas-gangrene antitoxin, each containing one therapeutic dose (or the equivalent in terms of prophylactic doses).

The Council were also charged with the responsibility of acquiring reserve stocks of certain vaccines and sera, to supplement supplies ordinarily available, for the control and treatment of epidemic diseases in the civilian population during wartime. The products in question were typhoid-paratyphoid, cholera and dysentery vaccines, and anti-anthrax, anti-dysentery, anti-plague and anti-typhoid sera. In the event, the need to use these materials for the control of epidemics did not arise, but it was necessary to augment existing stocks of typhoid-paratyphoid vaccine, and to plan for further production, following the decision of the Ministry of Health, late in 1940, to issue this vaccine free to local authorities for the immunisation of key personnel in the Civil Defence Forces.

Anti-anthrax serum, which was not made in this country before the war, presented a special problem, and in this case it was deemed advisable to supplement the existing reserves by arranging for its production on a limited scale.

In relation to the campaign inaugurated by the Ministry of Health towards the end of 1940 for the mass immunisation of children against diphtheria, as a protective measure of particular importance in wartime, the Council were asked at short notice to organise the supply and distribution of the necessary prophylactics. In the early months of the campaign very great difficulty was experienced in keeping pace with demands for material, but the rapid response of the home manufacturers, helped out by a generous gift from the American Red Cross Society, soon enabled supply to overtake demand. Thereafter the flow of production was maintained and adjusted in accordance with current requirements; but further steps had to be taken to deal with technical and administrative problems which arose, particularly in relation to the manufacture and testing of alum-precipitated toxoid, and to the determination of the optimum dosage for effective immunisation.

In 1941, at the request of the Service Departments and the Ministry of Health, the Council undertook to arrange for the supply and distribution of typhus vaccine required for the protection of Service personnel and of civilians specially exposed to the risk of infection. It was decided to obtain supplies of vaccine made by a method involving the use of fertile eggs and, as it was impracticable to manufacture such a vaccine in this country on a large scale, the necessary quantities had to be ordered from the United States and Canada. In making these arrangements the Council were greatly indebted for the assistance of the Rockefeller Foundation of New York.

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Towards the end of the war, the large-scale production of scrub-typhus vaccine was undertaken in this country, with the advice and assistance of members of the Council's staff (pp. 66 and 213).

The Council were also concerned to a certain extent, in association with the Ministry of Health, with arrangements for the supply of three other immunological products not ordinarily available commercially in this country. These were botulinum antitoxin, rabies vaccine, and human adult serum for the prophylaxis of measles in children.

With the exception of tetanus and gas-gangrene antitoxins, and scrub-typhus vaccine, distribution of all the products mentioned above to civilian Departments was made through the Emergency Public Health Laboratory Service during the war, and the machinery has been kept in operation until the present time.

In dealing with the many problems arising from these activities, the Council had the advice, particularly in regard to the preparatory work before the war, of the Emergency Immunological Supplies Committee (p. 424). They would wish to pay special tribute to the services rendered by Sir Percival Hartley of their staff, and to place on record their appreciation of the part played by the manufacturers—notably the Wellcome Foundation and the Lister Institute of Preventive Medicine—without whose ready co-operation the tasks set could not have been carried out.

The Emergency Public Health Laboratory Service

(Bacteriology and Epidemiology)

Organisation

The task of organising an Emergency Public Health Laboratory Service, to operate in the event of war, was assigned directly to the Medical Research Council by the Committee of Imperial Defence early in 1938. In planning the Service for England and Wales, the Council acted in consultation with the Ministry of Health and with the Air Raid Precautions Department of the Home Office: when the scheme took effect after the outbreak of war it was agreed that the Council should be regarded as acting on behalf of the Ministry, through which the necessary funds were thereafter provided. Corresponding arrangements were made by the Department of Health for Scotland, acting in consultation with the Council.

The object of the scheme was to augment existing facilities for public health diagnostic work, to meet the increased and special demands which were likely to arise under war conditions in Great Britain. There was reason to suppose that in time of war there might be great dislocation of sanitary services, resulting not only from air attacks but also from the general strain imposed by large-scale movements of the civil population and by concentrations of armed forces. Conditions might in various other ways be unusually favourable to the spread of epidemics. It was necessary, in particular, to envisage the possibility that the enemy might resort to deliberate attempts at bacteriological warfare, either from the air or by the use of secret agents. The need was all the greater because the provision for laboratory diagnosis and investigation in normal times left much to be desired, notably in the most vulnerable southern parts of England.

This deficiency was due to the manner in which public health administration had developed. Executive responsibility rested primarily with local authorities, administering communities which varied greatly in size and resources. Only

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the largest of these authorities could afford to maintain complete laboratory services of their own, and the others had to rely on their neighbours or on such assistance as could be obtained from laboratories intended primarily for other purposes. Some university laboratories, for instance, undertook routine work for neighbouring local authorities, but this function was naturally subordinated to the claims of teaching and research: it could not easily extend to the provision of a complete service, including constant availability for personal consultation and for participation in field investigations. Similarly, many hospital laboratories made examinations for public health purposes, but their main interest was of a different kind, relating to the diagnosis and treatment of the individual case rather than to preventive medicine. In other instances, medical officers of health had to depend on laboratories run on commercial lines and often at a distance, or upon local facilities of a very inadequate nature.

At the best, this system could not provide the advantages of a service organised on a national basis, with its opportunities for referring special types of examination to selected specialists elsewhere and its capacity to reinforce any particular laboratory in time of local stress. Most important of all, only a national service could provide an epidemiological intelligence network covering the whole country and so make possible effective action against sources of infection causing outbreaks not confined within administrative boundaries. A small central laboratory was indeed maintained by the Ministry of Health, but its activities were restricted to a few special types of work: the Ministry also regularly collected epidemiological information, but not necessarily supported by laboratory reports, and from time to time conducted special investigations.

It was in these circumstances that the Government decision was taken, and that the Council began to make necessary preparations some eighteen months before the war. The general principle was to utilise existing resources as far as possible, and to a large extent the Service came into being only on paper until the signal for action was given. Laboratory accommodation in universities, public schools and other institutions was earmarked. Bacteriologists normally engaged in teaching or research, together with the staff of the Ministry of Health Laboratory, were designated for the various posts. Arrangements were made to borrow some of the necessary initial equipment, notably from the London School of Hygiene and Tropical Medicine and from the Lister Institute, and the remainder was purchased and stored. Provision for transport was also made.

As a result of these preparatory measures, the Council were able to mobilise the Service immediately on the outbreak of war. The chief change that had subsequently to be made in organisation, on the basis of working experience, was in the location of laboratories, as detailed below. As the war went on there were naturally also many changes in personnel: research workers who could be spared at the outset had gradually to return to their normal employment as special wartime problems emerged; other bacteriologists were required by the Forces; Dr. F. Griffith and Dr. W. M. Scott, the two senior members of the pre-war Ministry of Health Laboratory, were killed by enemy action in 1941. These serious losses to the Service had to be replaced by new appointments from outside, and by the training within the Service of young medical men desirous of taking up public health laboratory work.

The greatest change, however, was in the functions of the Service as originally conceived. In the event, it was never called upon to deal with any major emergency due to war, and the results of continuous vigilance for evidence of bacteriological warfare or sabotage remained negative throughout. On the other hand, the laboratories were increasingly asked to undertake all

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the appropriate work required by local authorities in their vicinity (in return for a contributory payment based on peacetime expenditure for like purpose), and also investigations for military units. Thus, after the first few months, the laboratories came to be very fully employed, and many medical officers of health experienced for the first time the value of the scientific aid which a Service of this kind could bring to the diagnosis, control and prevention of infectious disease.

The Service not only aimed at a high level of laboratory work, using standardised technical methods, but also made a special feature of the availability of staff for personal consultation by medical officers of health and for participation in field inquiries when desired. Great attention was also given to the development of central reference laboratories to which special types of specimen could be sent by any unit of the Service. Epidemiological information was regularly reported to headquarters, and this greatly assisted the co-ordination of efforts for the control of outbreaks affecting wide areas, and the discovery of remote sources of infection.

The benefits of such a system are by no means static but should be cumulative in effect. The Council have naturally regarded the Service not merely as an instrument of routine but as a weapon of research. Organised investigations into epidemiological problems are capable of yielding important additions to fundamental knowledge as well as information of immediate utility. The object is not only to apply existing knowledge, but at the same time also to increase that knowledge and thus constantly to improve and extend the methods of preventive medicine.

Before the end of the war, therefore, the value of such a Service for normal needs had become fully apparent, and the Government decided in 1945 that the organisation should be continued on a permanent basis after the termination of the emergency scheme. The Council, for their part, accepted an invitation to remain responsible for the national Public Health Laboratory Service, when set up on its new permanent basis in England and Wales, at least during an initial period of five years.

Southern England

In planning the Service, attention was first given to the southern zone of England—roughly that part lying south of a line from the Wash to the Bristol Channel but excluding the Greater London area. Here the need was considered to be greatest and the existing facilities, in the main, least satisfactory. Two central laboratories were to be located at Oxford and Cambridge respectively, the former being designated as the technical and intelligence headquarters of the entire Service, with nine subsidiary laboratories elsewhere. The original list, with the names of the pathologists who were in charge at one time or another, was as follows:—

Oxford (Dunn School of Pathology, University)—Dr. W. M. Scott; Professor G. S. Wilson.
Cambridge (University Department of Pathology)—Dr. F. Griffith; Dr. A. W. Downie; Dr. E. T. C. Spooner; Dr. A. M. McFarlan.
Stamford (Stamford School)—Dr. R. Knox.
Holt (Gresham's School)—Dr. A. Q. Wells.
Colchester (Royal Eastern Counties' Institution)—Dr. P. H. Martin.
Canterbury (King's School)—Dr. A. M. McFarlan.
Horsham (Christ's Hospital)—Dr. J. C. Cruickshank; Dr. L. Foulds.
Winchester (Winchester College)—Dr. J. T. Duncan.
Sherborne (School for Girls)—Dr. E. P. Hicks.
Gloucester (No. 2 County Mental Hospital)—Dr. R. M. Fry.
Tavistock (Kelly College)—Dr. C. H. Andrewes.

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Of the above, only the laboratories at Oxford, Cambridge, Horsham and Winchester were retained throughout the war. The others were closed, mostly at an early stage, to permit of staff and equipment being used for the establishment of new laboratories in what proved to be more suitable localities, as follows:—

Norwich (Isolation Hospital)—Dr. A. Macdonald.
Ipswich (East Suffolk County Laboratory)—Dr. P. H. Martin.
Northampton (General Hospital)—Dr. L. Hoyle.
Leicester (Isolation Hospital)—Dr. R. Knox.
Reading (Royal Berkshire Hospital)—Dr. P. Kidd.
Exeter (Devon County Council Laboratory)—Dr. A. M. McFarlan; Dr. E. P. Hicks; Dr. J. C. Cruickshank.

(At Ipswich and Exeter the Service took charge of existing public health laboratories which continued to be controlled to some extent by the local authorities.)

In addition, the following permanent laboratories were at various dates associated with the Service, in respect of their public health activities, while retaining their autonomy:—

Peterborough (General Hospital)—Dr. D. H. Fulton.
Cambridge (Bacteriological Laboratory)—Dr. W. Harvey.
Eastbourne (Princess Alice Memorial Hospital) and Hellingly (East Sussex County Mental Hospital)—Dr. A. G. Shera.
Hastings (Royal East Sussex Hospital)—Dr. P. Lazarus-Barlow.
Brighton (Royal Sussex County Hospital)—Dr. L. R. Janes.
Worthing (32, Winchester Road) and Chichester (West Sussex County Laboratory and Royal West Sussex Hospital)—Dr. F. Standish.
Portsmouth (Royal Portsmouth Hospital)—Dr. J. A. D. Radcliffe.
Salisbury (General Infirmary)—Dr. L. H. D. Thornton.
Dorchester (Dorset County Laboratory)—Dr. T. V. Cooper.
Poole (Municipal Buildings)—Sir Robert Archibald.
Bristol (University Department of Preventive Medicine)—Dr. K. E. Cooper.
Plymouth (Prince of Wales's Hospital)—Dr. E. Wordley.

Midlands and North of England

The situation in this area was governed by the existence of six laboratories at university centres already undertaking a considerable amount of routine public health work, and these were associated with the Service, under the direction of their respective Professors of Bacteriology, as follows:—

Newcastle-upon-Tyne (King's College, University of Durham)—Professor E. M. Dunlop.
Manchester (University Public Health Laboratory)—Professor H. B. Maitland.
Liverpool (City Laboratories)—Professor Hedley D. Wright; Professor D. T. Robinson.
Leeds (University Department of Bacteriology)—Professor J. W. McLeod.
Sheffield (University Department of Bacteriology)—Professor Wilson Smith.
Birmingham (University Department of Bacteriology)—Professor J. F. D. Shrewsbury.

Arrangements were also made with these universities for the provision of constituent laboratories of the Service, as follows:—

Barnard Castle (Barnard Castle School)—Dr. S. H. Warren (Durham).
Kirkby Lonsdale (Grammar School)—Dr. J. W. Orr (Leeds).
Pocklington (Pocklington School)—Dr. W. Goldie (Leeds).
Lincoln (Technical College)—Dr. J. M. Croll (Sheffield).
Wellington (Wrekin College)—Dr. R. E. Jones (Birmingham).

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Of these, only the laboratory at Lincoln was permanently retained, but the following new laboratories were established instead:—

Northallerton (North Riding County Hall)—Dr. W. Goldie (Leeds).
Hereford (Herefordshire County Offices)—Dr. R. E. Jones (Birmingham).

In addition, the following permanent laboratories became associated with the Service at various dates:—

Carlisle (Cumberland Infirmary)—Dr. J. S. Faulds.
Wakefield (West Riding County Hall)—Dr. P. L. Sutherland.
Derby (Derbyshire County Offices)—Dr. J. L. G. Ireland.
Stafford (Staffordshire County Bacteriological Laboratory)—Dr. J. L. Edwards.
Birmingham (City Bacteriological Laboratory)—Dr. H. Henry.

Wales

North Wales was treated in the original plan as part of the foregoing area by the provision of the following laboratory from the nearest university centre:—

Conway (Fisheries Experiment Station)—Dr. D. T. Robinson (Liverpool); Dr. E. D. Hoare.

This was retained throughout, but the initial dependence on Liverpool was latterly discontinued.

South Wales was provided with one central and one subsidiary laboratory, as follows:—

Cardiff (Institute of Preventive Medicine, Welsh National School of Medicine)—Dr. V. D. Allison.
Aberystwyth (Dairy Research Institute, University College; later removed to Cardiganshire General Hospital)—Dr. A. C. Jones; Dr. Marjorie V. N. Sudds.

These were retained throughout, and the following new laboratory was later opened:—

Carmarthen (Penlan Road)—Dr. R. M. Fry.

In addition, the following permanent laboratory became associated with the Service:—

Swansea (Beck Laboratory, General Hospital)—Dr. A. F. Sladden.

Greater London

It had from the outset been assumed that London would be unsuitable as a wartime headquarters of the national Service (apart from administration from the Council's office), but the needs of Greater London had still to be considered as a local problem. The arrangement made was that each of the ten Hospital Sectors of the Emergency Medical Service should provide a public health laboratory in the peripheral zone. These laboratories were included in the plans made by the Council, as follows:—

Brentwood (Brentwood School)—Dr. A. B. Rosher (London Hospital—Professor S. P. Bedson).
Hertford (Haileybury College)—Dr. A. W. Downie (London Hospital—Dr. P. N. Panton).
Harpenden (Rothamsted Experimental Station)—Dr. J. M. Alston (St. Bartholomew's Hospital—Professor G. Hadfield).
Watford (Peace Memorial Hospital)—Dr. A. R. Berrie (University College Hospital—Professor A. A. Miles).
Northwood (Merchant Taylor's School)—Dr. C. J. C. Britton (Middlesex Hospital—Professor J. McIntosh).
Ealing (adjoining King Edward VII Memorial Hospital)—Dr. A. B. Porteous (St. Mary's Hospital—Professor A. Fleming).
Slough (Horlicks Limited)—Dr. G. W. Goodhart (Westminster Hospital—Dr. R. J. V. Pulvertaft).

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Guildford (County Secondary School for Girls)—Dr. R. F. L. Hewlett (St. Thomas's Hospital—Dr. J. Bamforth).

Epsom (Epsom College)—Dr. T. C. Stamp (King's College Hospital—Dr. E. ff. Creed).

Downe (Buckston Browne Laboratories of the Royal College of Surgeons)—Dr. J. C. Colbeck (Guy's Hospital—Professor G. Payling Wright).

On the outbreak of war it was agreed that these laboratories could more conveniently be administered as part of the Hospital Sectors to which they belonged, and they accordingly came under the direct control of the Ministry of Health instead of that of the Council, and they were merely associated with the Emergency Public Health Service for purposes of intelligence. Subsequent changes in location and personnel, therefore, need not be here recorded.

It remains to mention that during part of the war certain functions of a central laboratory of the Service, otherwise performed at Oxford, were carried out in the London School of Hygiene and Tropical Medicine.

Scotland

As already stated, the Council gave advisory help in planning the corresponding arrangements in Scotland, but the executive responsibility lay with the Department of Health. The emergency arrangements were based on a different principle, adapted to the special conditions prevailing. From the outset they incorporated the existing facilities in a single whole. This was possible because bacteriological work in Scotland was already organised on a regional basis, with the four university cities—Edinburgh, Glasgow, Dundee and Aberdeen—as the chief centres: a fifth region was centred on Inverness. The main laboratories at these centres were supplemented by subsidiary ones elsewhere, and by a small number of transportable units which could be despatched to the more remote districts if required. As the Council were not concerned with the details of the scheme, these do not fall to be recorded here.

Reference Laboratories

From the beginning, one of the features of a service organised on a national basis was the provision of Reference Laboratories to which specimens could be sent from all over the country for certain special kinds of examination. The principal Reference Laboratories maintained during the war period were:—

Enteric Reference Laboratory (*for Vi-agglutination tests of suspected carriers and Vi-phage determination of strains of typhoid and paratyphoid bacilli*) : successively at the Oxford laboratory of the Service, at the National Institute for Medical Research, and at the Wellcome Research Institution, London—Dr. A Felix.

Streptococcus Reference Laboratory (*typing of Group A streptococci*) : Cambridge Laboratory of the Service, and Queen Charlotte's Hospital, London—the late Dr. F. Griffith ; Dr. S. D. Elliott.

Salmonella Reference Laboratory (*typing*) : at the Oxford laboratory of the Service—the late Dr. W. M. Scott ; Dr. Joan Taylor.

Bacterial Sabotage Reference Laboratory (*examination of suspected material*) : National Institute for Medical Research, London—Mr. P. Bruce White.

Chemical Reference Laboratory (*chemical examination of water, milk and sewage*) : successively at the Oxford laboratory of the Service and at the London School of Hygiene and Tropical Medicine—Professor M. E. Delafield.

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The following members of the Service also acted, in addition to their other duties, as specialist referees:—

Anthrax infections—Dr. V. D. Allison; *Brucella infections* (*cultural and serological tests*)—Professor G. S. Wilson; *Diphtheria* (*serological typing*)—Dr. D. T. Robinson; *Pathogenic Fungi*—Dr. J. T. Duncan; *Horseflesh* (*identification*)—Dr. A. W. Downie; *Meningococci* (*typing*)—Dr. Joan Taylor; *Plague*—Dr. V. D. Allison; *Pneumococci* (*typing from epidemics*)—Dr. A. W. Downie, Dr. V. D. Allison; *Smallpox* (*serological tests*)—Dr. A. W. Downie; *Staphylococci* (*bacteriophage typing*)—Professor G. S. Wilson; *Staphylococci* (*serological typing*)—Dr. E. H. Gillespie, Dr. Betty Hobbs; *Tetanus bacilli*—Dr. A. W. Downie; *Trichinosis* (*examination of rats or pigs*)—Dr. V. D. Allison; *Tubercle bacilli* (*typing*)—Dr. A. Q. Wells; *Typhus* (*serological tests*)—Dr. A. Felix.

In addition, the Service had the co-operation of the following experts in a similar capacity:—

Anaerobes—Professor A. A. Miles, University College Hospital, London; *Anthrax*—Professor Hedley D. Wright (the late), University of Liverpool; *Cholera vibrios*—Mr. P. Bruce White, National Institute for Medical Research; *Dysentery bacilli* (*typing*)—Lt.-Col. R. F. Bridges, Standards Laboratory, Oxford, *Entomological specimens*—Professor P. A. Buxton, London School of Hygiene and Tropical Medicine; *Helminthological specimens*—Professor R. T. Leiper, London School of Hygiene and Tropical Medicine; *Influenza* (*serological tests*)—Dr. C. H. Andrewes, National Institute for Medical Research; *Leptospiral infections* (*agglutination tests*)—Professor A. D. Gardner, University of Oxford; *Psittacosis*—Professor S. P. Bedson, London Hospital; *Staphylococci* (*enterotoxin production*)—Dr. J. C. Colbeck, E.M.S. Laboratory, Downe, Kent; *Tubercle bacilli* (*typing*)—Dr. J. A. Young, University Field Laboratories, Cambridge; *Virus infections of the central nervous system* (*other than poliomyelitis*)—Dr. J. E. Gordon, Harvard Hospital Unit, Salisbury.

Research Work

For descriptive purposes, the research work undertaken by the Service may be divided into two categories: (*a*) Group research; (*b*) Individual or team research. By group research is meant work carried out on the same subject by two or more laboratories; by individual or team research is meant work carried out on a given subject by one or more workers in the same laboratory.

The constitution of the Service lent itself admirably to group research, and numerous problems were investigated in this way. Before describing them, it may be well to point out the virtues of the group method of inquiry. Its greatest value lies in the rapid collection of data when these are urgently required. The use of a relatively standard technique by twenty laboratories, for example, enables information to be obtained in a very much shorter time than would be necessary if the inquiry were restricted to any one laboratory. Examples in point, which will be dealt with more fully below, are the distribution of bovine tubercle bacilli in cases of non-pulmonary tuberculosis and the frequency and types of *Salmonella* in dried egg. Another advantage is that the data collected from several laboratories are more likely to be representative of the country as a whole than those obtained by any of them individually. For instance, in the non-pulmonary tuberculosis survey striking and significant differences were found between the distribution of bovine tubercle bacilli in different parts of the country; generalisations drawn from the Newcastle, Carlisle, Stafford, Oxford, Cambridge, or Exeter laboratories separately would have been misleading. Only by a survey embracing the whole country was it possible to obtain a true picture of the amount of disease caused by this type of bacillus. Another example is afforded by the

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survey into the type distribution of diphtheria bacilli, which showed not only that different types predominated in different parts of the country, but that in any one part of the country the prevailing type tended to be replaced in time by another type.

A further advantage of the group research method is that it tends to reveal the importance of predisposing or secondary factors in the causation of disease. The frequency, for example, of cross-infections in hospitals is determined by a number of different factors, such as the construction of the wards, the number of patients in the ward, the duration of stay in hospital, the nursing technique and so on. By making observations in different hospitals in different places, it is possible to assess to some extent the part played by secondary factors of this type, and to draw conclusions that might be different from those based on observations made in one or two hospitals only. This was revealed by the scarlet fever inquiry referred to below. Again, in assessing the value of prophylactic vaccination against a disease such as whooping cough, it is an advantage to be able to immunise children living in different environments and in different parts of the country. A vaccine, for example, of relatively weak antigenic potency may be sufficient to protect the children of the higher social classes or children living at home under good conditions, but may fail to do so in children living under overcrowded conditions or in residential nurseries, where the risk of repeated and more concentrated infection is greater.

The investigation by several laboratories of a disease, such as infantile enteritis, that presents a more or less similar clinical picture throughout the country, may reveal a diversity of causative agents. Some outbreaks, for instance, may be caused by a member of the dysentery group, others by a member of the food-poisoning group, others may be associated with infection with *Giardia lamblia,* and others may appear to be caused by a virus. Premature conclusions, based on the examination of insufficient or unrepresentative material, are likely to be avoided only by widespread, co-ordinated studies.

One last advantage of the group research method is that, if several different workers are investigating a problem and pooling their results, one of them may quite easily discover a much better technique for its approach than has been previously used, and this may be made immediately available to the other laboratories. An example of this type was afforded by the dried egg inquiry (p. 174).

Group Research Investigations

1. *Non-pulmonary tuberculosis.*—The main purpose of this inquiry was to find out whether the rise in the non-pulmonary tuberculosis death rate during the early years of the war, to which attention was drawn by the Council's Committee on Tuberculosis in Wartime (see p. 69), was caused by the bovine or the human type of tubercle bacillus. A conference was held of English, Welsh and Scottish representatives, and it was decided that an investigation along similar lines should be carried out by each country separately. The results, which are now complete, are being prepared for publication.

In England, material provided by hospital pathologists in different parts of the country was examined at 25 typing centres. In addition, information was obtained on factors, such as the age, sex, and occupation of the patient, on recent change of residence, on the milk supply, and on contact with open cases of tuberculosis, which might have had a bearing on the genesis of the disease. The information obtained in this way has shown that, with the possible exception of bone and joint disease, the bovine type of tubercle bacillus is apparently responsible for much the same proportion of non-pulmonary

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tuberculosis as before the war; that infection with the bovine type is much more frequent in some parts of the country than in others, particularly in the North-Midland and North-Western regions; that, apart from the first five years of life, when the incidence is the same in both sexes, the proportion of bovine to human type infections increases progressively in females with age, till in the group 15 years and over it is approximately double that in males; that, in contrast to previous experience, the maximum incidence of infection with the bovine type of bacillus is now in the 5-9 instead of the 0-4 year age group, suggesting that the greater care in infant feeding has resulted in the partial protection of the pre-school child, but that the introduction of the milk-in-schools scheme, without adequate measures to safeguard the purity of the milk, may have led to the increase in the proportion of bovine infections in older children; and that the raw milk supply of the country appears to be almost as heavily contaminated with tubercle bacilli now as it was 20 years ago. The value of this information for supporting the introduction of compulsory pasteurisation of all but T.T. milk needs no stressing.

2. *Cerebrospinal meningitis.*—Between December, 1939, and April, 1941, several studies of the meningococcal carrier condition in the nasopharynx were made in the laboratories of the Service at Cambridge, Cardiff, Colchester, Horsham, Tavistock and Wellington. The subjects examined were soldiers under training, living either in barracks, requisitioned schools or offices, or billeted in private houses. The plan of the investigations differed in each area; for example, at Cambridge two groups of 88 and 61 soldiers billeted in private houses were swabbed on three or more occasions, with control groups of medical students and laboratory staff. In Cardiff 100 soldiers aged 37-58 years, billeted in offices, were swabbed at fortnightly intervals for one year, and 100 recent recruits aged 20-22 years, billeted in a school, were swabbed fortnightly for 3 months. At Horsham 46 soldiers in barracks at Aldershot were swabbed thrice weekly for four weeks. At Wellington, Tavistock, and Colchester nasopharyngeal swabs were taken once from many hundreds of soldiers, in batches of 30 to 100 at intervals over a period of from 4 to 8 months.

All meningococci isolated were studied serologically and placed in one of the following five categories:—Group I, Group II, Group I + II, Feeble Agglutinators and Inagglutinable. Owing to varying conditions in the different areas it proved impossible to combine the results. In most of the studies the meningococcal carrier rate in the nasopharynx was high, ranging from 33 to 82 per cent. The proportion of Group I meningococci isolated varied from 13 to 60 per cent. on different occasions, but in every study Group I meningococci constituted the majority of the strains isolated.

In Cardiff it was noted that, between January and June 1940 (the peak period of the epidemic of cerebrospinal meningitis), the Group I carrier rate was 17.3 per cent., but that from July onwards it dropped to 9.1 per cent. Over a period of twelve months meningococci were isolated on one or more occasions at fortnightly swabbings from 91 out of 102 men (89.2 per cent.) and Group I organisms from 74 men (72.5 per cent.). No case of cerebrospinal meningitis occurred among the soldiers investigated or among their contacts during the period of study, confirming previous experience that meningococcal infection of the nasopharynx is very common during epidemic times, but that only a very small proportion of infected persons develop meningitis.

Studies were also made on the methods of keeping meningococci alive during transport of specimens to the laboratory, and on the effect of adding *p*-aminobenzoic acid to culture media when examining cerebrospinal fluid from patients under sulphonamide treatment.

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3. *Combined active and passive immunisation against diphtheria.*—Though the prophylaxis of disease by combined active and passive immunisation is well established in veterinary practice, it is only within recent years that its application to human medicine has been seriously considered. A review of the literature revealed a surprising conflict of opinion on its value, and it was felt that careful quantitative observations were required, preferably on the human subject. An agreed plan of inquiry was drawn up, and observations were made on a total of about 400 undergraduate medical students at Oxford, Cambridge, Sheffield, and Liverpool. The antitoxin content of the blood was compared at intervals before and after inoculation in students receiving alum-precipitated toxoid (A.P.T.) alone, and in those given a dose of antiserum at the same time. The general results showed that in the latter group, provided only a small dose (500 units) of serum was injected, the development of antitoxin was rather slower than in the group receiving A.P.T. only, but that the ultimate concentration in the blood was not significantly different from that in the first group. If, however, a large dose (5000 units) of serum was injected, not only was there a delay in the appearance of antitoxin in the blood, but the ultimate concentration reached was less than in the group receiving active immunisation alone.

Field observations carried out at Oxford established the value of combined active and passive immunisation in the control of institutional outbreaks of diphtheria. It was found that, if all children were given simultaneous injections of A.P.T. and 500 units of antitoxin, followed four weeks later by a second dose of A.P.T., and if all carriers of the diphtheria bacillus were segregated for six weeks, an outbreak could be brought to an abrupt end without the necessity of closing the school. This method proved most successful in practice, thus confirming the scientific basis on which it rested.

4. *Distribution of different types of diphtheria bacilli.*—Data collected during the years 1941 to 1944 by a number of constituent and associated laboratories of the Service provided information on the distribution of the different types of diphtheria bacilli throughout the country. The *gravis* type constituted about 45 per cent. of all strains studied. It was usually the commonest type, but in some areas the *mitis* or *intermedius* type predominated. Although the type distribution did not vary greatly during these years, a significant rise in *gravis* type infections was recorded by the Leeds, Lincoln, Northampton, Winchester, Bristol, Cardiff, and Carmarthen laboratories, and a significant fall by the Liverpool, Leicester and Exeter laboratories. Where it was possible to correlate changes in the morbidity and case-fatality rates with changes in type distribution, it was found that a rise or fall in the frequency of *gravis* infections was accompanied by a similar trend in the case-fatality rate.

5. *The incidence of cross-infections, complications and return cases in scarlet fever.*—In view of the importance of cross-infection in surgical wards revealed by hospital bacteriologists in the early years of the war (p. 37), it seemed of interest to find out what part cross-infection played in the causation of complications and of return cases in scarlet fever. A joint investigation was organised at Oxford, Cambridge, and Cardiff, in which repeated cultures were made on patients in scarlet fever wards, followed by determination of the serological type of the infecting organism. The results showed the danger of generalisation from observations made in any one environment at any one time. Not only did the type-distribution of *Streptococcus pyogenes* vary in the three centres, but the incidence of cross-infection was twice as high in Cardiff as in Oxford. Moreover, the results differed greatly from those

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obtained in a similar investigation by Allison and Brown in London before the war, as can be seen by the following figures:—

	Allison & Brown's experience in London before the war	*Oxford, Cambridge and Cardiff experience during the war*
Cross-infection rate	70 per cent.	24 per cent.
Complication rate	43 ,,	16 ,,
Proportion of complications attributable to cross infection ...	90 ,,	30 ,,
Return case rate	4·9 ,,	2·1 ,,

It will be seen that, in the hospitals included in the wartime study, 70 per cent. of complications were due to the primary infecting type, and that cross-infection played a relatively small part in their causation. Analysis of the figures revealed also that the majority of complications due to cross-infection occurred from the third week onwards of the patient's stay in hospital. One of the chief conclusions reached, therefore, from this investigation was that, wherever possible, scarlet fever patients should be discharged from hospital within three weeks. Other studies of problems of hospital cross-infection, promoted by the Council during the war years, are mentioned on pp. 195-6.

6. *Neonatal diarrhoea.*—This apparently uncommon disease attacks newborn infants, sometimes with almost lightning rapidity, and is accompanied by a high case-fatality rate. Arrangements were made at Oxford and Cambridge for a qualitative and quantitative bacteriological study of the faecal flora of healthy contact and non-contact babies, and of babies suffering from the disease. In healthy non-contact babies, lactobacilli constituted about 80 per cent. of the flora and coliform bacilli only about 10 per cent. In sick babies the proportions tended to be reversed; but little diagnostic weight could be placed on these findings, since the same tendency was present in healthy contact babies. No evidence was obtained to show that any known pathogenic organism or any known soluble toxin of bacterial origin was responsible for the disease. Further investigations, with particular reference to the possibility of a virus infection, are now being carried out.

7. *Bacteriology of dried egg.*—By 1941 it had become clear that, unless some protein of animal origin was added to the national dietary, serious danger of malnutrition might arise. The Ministry of Food therefore decided to import spray-dried egg from America on a large scale. The first retail distribution of this substance to the general public took place in July, 1942. Examination of the new product soon revealed that a proportion of it was contaminated with organisms of the *Salmonella* or food-poisoning group. The advice of the Council was sought, and an Advisory Bacteriology Committee, with one of the Council's representatives in the chair, was set up to help the Ministry of Food in the prevention of disease which might be caused by eating the contaminated material. Arrangements were at once made for the examination of a large number of samples of dried egg by the Ministry of Food's Laboratory at Cambridge, and by several of the constituent laboratories of the Service, so as to obtain as rapidly as possible information on the frequency and types of salmonellae present. At the same time a reference laboratory for the determination of *Salmonella* types was established at Oxford. The results were of great bacteriological and practical interest. It was found that 10 per cent. of samples of dried egg contained salmonellae, and that the salmonella strains isolated belonged to 33 different serological types, the majority of which were new to this country. Following the retail distribution of dried egg, the number of *Salmonella* outbreaks of food poisoning in England and Wales reported to the

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Service increased from 104 in 1942 to 454 in 1944. The majority of these outbreaks were caused by types of *Salmonella* that had not previously been encountered here. Comparison showed, moreover, that the six commonest types responsible for food poisoning were the same as the six commonest types found in dried egg. The bacteriological and epidemiological evidence combined left no doubt that much of the increase in food poisoning from 1942 onwards was ascribable to infection from the new product. Early recognition of the danger enabled the Ministry of Food to take precautions and issue instructions designed to minimise the extent and severity of outbreaks of food poisoning due to this cause, and so avoid what might have resulted in a very difficult situation. A full account of the work has been published in the Council's *Special Report Series* No. 260.

8. *Infective hepatitis.*—In May, 1943, the Council, acting on a request from the Ministry of Health, and in consultation with the War Office, organised an investigation into the causes of the increased incidence of different forms of jaundice which were prevalent in England and abroad at that time. For this purpose, a special Jaundice Committee was appointed, with Professor L. J. Witts as Chairman and Dr. A. M. McFarlan as Secretary; in addition, Dr. McFarlan and Dr. M. R. Pollock were seconded from the Emergency Public Health Laboratory Service to serve as members of the Council's Jaundice Team. Mention has already been made on pp. 66-68 of the composition of this team, and also of certain aspects of its work. The Cambridge E.P.H. Laboratory, under Dr. A. W. Downie and later Dr. E. T. C. Spooner, undertook to do such routine bacteriology as was considered relevant.

The epidemiological studies particularly entrusted to Dr. McFarlan were carried out among both civilian and military groups in Civil Defence Region IV (from the Wash to the Thames, in the Eastern half of England), where the disease was made notifiable in November, 1943. Inquiries indicated that the incidence of the disease had reached its peak in the region shortly before the investigation began, but the figures collected for 1944-45-46 have supported the theory of a regular seasonal trend, with a peak in the autumn-winter period. In the civilian population, the incidence rate was 0.5 to 2.0 per 1,000 population, though this increased to 55 per 1,000 in children of school age in one outbreak. The disease was rare in children under 5 years of age. Studies were also made of outbreaks that began in certain military units of the British Army in Sicily and continued after their return to Great Britain some months later. These outbreaks were very similar to those occurring in the civil population, with numerous instances of 20- to 40-day intervals between the onset of illness in contacts. The attack rate in troops in the Mediterranean was higher than in troops in Great Britain, but there was nothing to show that the "Mediterranean" strain was more pathogenic or infective than other strains. There was no evidence of spread of infection by water, milk or food. Dr. McFarlan and Dr. Pollock studied a large outbreak in an institution for mental defectives, where Dr. Pollock, using various techniques for the detection of liver damage, was able to diagnose cases as early as 10 days before the onset of jaundice, while the total serum bilirubin was still normal. By using Hunter's test for bilirubin in the urine of contacts in a nursery outbreak, Dr. Pollock found a very small proportion of completely symptomless cases of hepatitis. Abnormal results with the bromsulphthalein excretion test were the earliest constant abnormality found. One patient showed abnormal retention of the dye when first tested 16 hours after the onset of symptoms. These studies also facilitated the collection of material from patients early in the disease for transmission experiments in animals and man.

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Dr. Pollock also collaborated with Dr. (then Major) Clifford Wilson and others in examining the therapeutic effects of methionine, cysteine, and of low and high fat diets, in groups of military patients with hepatitis. Other members of the team studied the blood picture and serological reactions of patients with various types of acute liver disease, and investigated the blood and excreta of patients with infective hepatitis, arsenotherapy hepatitis and homologous serum jaundice for the presence of virus (p. 68). The problems of the aetiology and frequency of homologous serum jaundice, especially in relation to transfusion, are discussed further on pp. 191-2.

9. *Infection of cattle with Brucella melitensis.*—The isolation by the Stafford laboratory in 1940 of a strain of *Brucella melitensis* from cows' milk occasioned both surprise and misgiving. The organism responsible for contagious abortion of cattle in Great Britain is *Br. abortus,* and no indigenous infection of animals or man with *Br. melitensis* had ever been recorded. Suspicion was aroused by the finding that the herd in question had been inoculated with a vaccine prepared by a firm known to have obtained some of its original material from Germany, and it was feared that widespread bacterial sabotage might be attempted. The Oxford laboratory, working in conjunction with the Ministry of Agriculture's laboratory at Weybridge, was asked to investigate a number of other herds into which animals from the infected herd, which had just been sold, had been introduced. Several hundred samples of milk from individual quarters of the udder were examined, with the result that two further herds were found to be infected with *Br. melitensis.* All the animals in these herds, as well as those in the original herd, were slaughtered, the supply of the suspected vaccine was stopped, and milk from all herds under investigation was sent to pasteurizing depots. No further trouble was experienced, and no strain of *Br. melitensis* had up to the end of 1946 been subsequently isolated from either animals or man.

Individual and Team Research

For the sake of brevity it will be convenient to describe these investigations under general headings.

Enteric infections.—The discovery by Felix before the war of the Vi antigen of the typhoid bacillus, and by Craigie of a method of classifying typhoid bacilli into types by means of a series of bacteriophages acting on the Vi antigen, provided a valuable tool for studing the epidemiology of typhoid fever. At the outset of the war Dr. Felix was placed in charge of an Enteric Reference Laboratory to which strains of typhoid bacilli from any part of Great Britain could be sent for typing. The work carried out by this laboratory proved to be of outstanding value. With its help it was possible to show that, in some outbreaks, cases of typhoid fever scattered in different parts of the country but due to the same Vi-phage type of bacillus had been infected from a common source. In this way success was achieved not only in tracking down the source of origin, but in proving beyond doubt that a particular carrier was responsible for the contamination of a given article of food—a feat which epidemiological investigation alone would have been powerless to perform.

A further extension of this work lay in the application of the Vi-agglutination test to the detection of chronic carriers. It was found that about 90 per cent. of chronic carriers of typhoid bacilli had Vi-agglutinins in their blood serum. In searching for a chronic carrier who was believed to be responsible for an outbreak of typhoid fever, it was therefore found advisable to examine the serum of all suspected persons for Vi-agglutinins before undertaking routine cultivation of the faeces and urine. The practical value of

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this test is enhanced by the fact that it is independent of the intermittency of excretion. The test is also of service in indicating whether a given typhoid convalescent patient is likely to become a chronic carrier. If the titre of Vi-agglutinins remains steady or rises during the six weeks following the patient's discharge from hospital, the possibility of his becoming a chronic carrier has to be envisaged; if, on the other hand, Vi-agglutinins are absent or fall in titre during this period, it is usually safe to predict that the patient has ceased to excrete typhoid bacilli or will very soon do so. This practice is now being recommended for general application to convalescent typhoid fever patients throughout the country.

Research work undertaken by Dr. Felix during the war led to the finding of Vi-antigens in the paratyphoid B bacillus and in *Salmonella typhi-murium* —one of the commonest organisms met with in food poisoning; it also resulted in the development of a series of bacteriophages acting on the Vi-antigen, by which a subdivision into types, similar to the Vi-phage types of the typhoid bacillus, could be effected. Already this method of typing has proved of value in the epidemiological investigation of outbreaks of paratyphoid fever.

An interesting application of the Vi-phage method of typing was its use by workers at the Cardiff laboratory for revealing the origin of contamination of water or sewage with typhoid or paratyphoid bacilli. In one case, for example, it proved possible to trace back the source of typhoid infection in a boy, who drank water from a polluted stream, *via* water, sewage effluent, crude sewage, and faecal specimens to unsuspected typhoid carriers in a large institution.

The practical application of the discovery of the Vi-antigen was not limited to diagnosis. In 1941 Dr. Felix introduced a method of preparing typhoid-paratyphoid (T.A.B.) vaccine in which the activity of the Vi-antigen was preserved. The current method of killing the organisms by heat and protecting the vaccine from contamination by the addition of 0.5 per cent. phenol led to a considerable destruction of the Vi-antigen. Dr. Felix, however, found that, if the organisms were killed and preserved from contamination with 25 per cent. alcohol, a large proportion of the Vi-antigen remained intact. Observations carried out by four of the constituent laboratories showed that the disinfectant action of 25 per cent. alcohol on a variety of organisms was slightly greater than that of 0.5 per cent. phenol, thus disposing of the criticism that the alcoholised vaccine was unsafe for use. After field trials had been carried out in the Service on the degree of reaction and of antibody response, the new alcoholised vaccine was substituted for phenolised vaccine in the Army, the R.A.F., and civilian practice.

The importance attached by the Service to the early diagnosis of cases of enteric fever and of food poisoning, and to the detection of healthy carriers, afforded a stimulus to the development of improved media for the cultivation of organisms of the *Salmonella* group. Dr. Hoyle at Northampton devised a useful medium containing brilliant green and acid fuchsin, and Dr. Knox, Dr. Gell, and Dr. Pollock at Leicester one containing eosin, brilliant green, and methylene blue. Of greatest interest, however, was the finding by workers in the Leicester laboratory that the selective action of sodium tetrathionate lay in its utilisation as a hydrogen acceptor by organisms of the *Salmonella* group. The reduction of tetrathionate by these organisms affords a basis for a valuable enrichment medium containing this substance.

Another medium for the enrichment of *Salmonella*, having the particular virtue of suppressing the growth of *Proteus*, was introduced by Dr. R. E. Jones and Mr. Handley at Hereford. It depended on the use of a quinone compound —preferably cacotheline. It proved superior to other media for the isolation

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of *Salmonella* from material, such as the mesenteric lymph nodes of pigs, that was liable to heavy contamination with organisms of the *Proteus* group.

Numerous studies were made by individual laboratories of outbreaks of enteritis among young children in residential nurseries, schools, and similar institutions. In some of these outbreaks dysentery bacilli of the Sonne or Flexner type were found, and in others organisms of the *Salmonella* group. In a number of instances, however, no bacteriological agent could be incriminated. Studies by members of the Oxford laboratory showed that, in some outbreaks of this last group, infection with the protozoon, *Giardia lamblia*, was apparently responsible. Treatment with mepacrine resulted in rapid elimination of the organism from the intestine, with cessation of the diarrhoea and corresponding improvement in the child's general condition.

Food poisoning.—The study of food poisoning due to the *Salmonella* group of organisms, and its increased prevalence following the retail distribution of spray-dried egg, have already been referred to (p. 174). During this investigation six new types of *Salmonella* were discovered—*Salm. cardiff, Salm. norwich, Salm. horsham, Salm. cambridge, Salm. shoreditch*, and *Salm. chittagong*.

Apart from salmonella infection, there was a big increase in the number of outbreaks of food poisoning attributable either to enterotoxin production by *Staphylococcus aureus* in the food, or to toxic substances of undefined nature formed apparently as the result of growth in the food of other species of bacteria.

At Oxford Dr. F. Fulton made a critical study of staphylococcal enterotoxin, and was able to show that the usual method of demonstrating the presence of this substance by injection of kittens was unreliable. He also proved that the enterotoxin was different from the β-lysin, with which some previous workers had identified it. Fractionation studies, controlled by experiments in human volunteers, indicated that the enterotoxin was a proteolytic enzyme, similar in some respects to the lecithinase of *Cl. welchii*.

Another advance made in the investigation of staphylococcal infections—not limited to food poisoning—was the development at Oxford of a method of subdividing staphylococci into types by use of a series of specific bacteriophages. Since 40 per cent. or so of healthy persons carry *Staph. aureus* in the nose or on the skin, it is usually impossible to be certain that any one of a number of food handlers is responsible for contaminating a given food. By the phage-typing method, however, it could often be shown that a given type of staphylococcus was present in the vomit of the patients, in the incriminated food, and in one only of the persons who had taken part in the preparation of the food, thus revealing the human origin of the contamination.

Useful work was also carried out on the coagulase reaction and on the production of staphylococcal haemolysin.

The type of food-poisoning outbreak in which neither salmonella bacilli nor staphylococci could be incriminated presented a very difficult problem. The evidence collected by a number of individual laboratories suggested that growth in the food of some non-pathogenic bacteria, if it was sufficiently heavy, was accompanied by the formation of toxic substances of undefined nature having an irritant effect on the gastro-intestinal mucosa. Organisms of the aerobic and anaerobic spore-bearing groups came specially under suspicion. Soups, gravies, and custards that had been prepared on the previous day, and left overnight at a temperature suitable for bacterial multiplication, were sometimes found to contain enormous numbers of one or other of these groups of organisms. Whether the toxic substances were formed by the breakdown of protein in the food or were more closely related to the

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bacterial cell itself was not determined. The findings serve to emphasise the importance, particularly in communal feeding, of taking every precaution to limit bacterial growth of any kind in the food.

At Leicester, after three outbreaks of this type had occurred in schools served by a communal kitchen, Dr. Knox, assisted by Mrs. Walker, carried out, at the request of the Ministry of Education, an investigation into the best methods for cleaning and sterilising the large food containers that were suspected of causing contamination of the food. It was found that the containers themselves became heavily contaminated during the washing-up process, and that if a suitable detergent in hot water, followed by proper rinsing and drying with a clean towel, were used, the greater part of the contamination could be avoided.

Staphylococcal infections in maternity homes.—Pemphigus and conjunctivitis in the babies, and breast abscesses in the mothers, were frequently met with in maternity homes. The use of the serological and, still better, the phage method of typing staphylococci sometimes led to the identification of a nurse, a midwife, or in one instance a matron, as the source of infection. Once introduced, the organisms seemed to spread principally in the nursery, where babies were often laid side-by-side in a confined space and looked after under conditions that favoured the rapid spread of cross-infection. Nearly all the evidence pointed to the nursery as being the chief focus of infection. Mothers tended to be infected by the babies, not the reverse; and examination of breast milk, even in the absence of obvious mastitis, frequently revealed very heavy contamination with staphylococci.

Diphtheria.—Mention has already been made of the group research on university students into the scientific basis of combined active and passive immunisation. The control of diphtheria presented a serious problem in the early years of the war, and the attention of the Oxford workers, in particular, was directed towards its solution. Groups of school children were injected with alum-precipitated toxoid (A.P.T.) made by different manufacturers, and the results assessed by measuring the Schick-conversion rate. It was found that two doses of 0.1 and 0.3 ml. at 4 weeks' interval of Burroughs Wellcome's A.P.T. resulted in a Schick-conversion rate of about 98 per cent. When free immunisation against diphtheria was introduced by the Ministry of Health in 1941, this firm was temporarily unable to supply all the A.P.T. required for the purpose, and a product of different origin was used to some extent. Observations by the Oxford laboratory soon revealed that the Schick-conversion rate in children immunised with this other product was only 68 per cent., and the batch of A.P.T. was withdrawn as quickly as possible.

The poor antigenic potency of this batch was remarkable, since it had passed the official tests laid down under the Therapeutic Substances Act. This led to an investigation by Sir Percival Hartley, at the National Institute, into the reason for the failure of the official tests. Several batches of A.P.T. of different origin were tested on guinea-pigs at Hampstead and on children at Oxford, with the result that Sir Percival Hartley was able to devise more stringent conditions for the control of the antigenic potency of A.P.T. It was clear, however, that the behaviour of any given batch in children must remain the final criterion of antigenic potency.

The introduction of sulphonamide and penicillin snuffs by Delafield, Straker, and Topley at the London laboratory of the Service opened the way for the treatment of carriers of diphtheria bacilli. It was soon found that the use of sulphathiazole snuff led to the rapid disappearance of diphtheria bacilli from the noses of even long-standing carriers, and provided a singularly effective method of curing the nasal carrier and, to a less extent, the nose and

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throat carrier. Pure throat carriers, however, proved resistant; for them tonsillectomy has so far presented the only satisfactory method of treatment.

Other work on diphtheria included the development of a new tellurite-blood agar medium by Dr. Hoyle, while working in the Cardiff laboratory; it is now widely used. Dr. Hoyle also made a study of the antigenic structure of diphtheria and diphtheroid bacilli, and demonstrated the presence in them of three different lipoid antigens detectable by the complement-fixation test.

Whooping cough.—As soon as diphtheria immunisation seemed to be established on a satisfactory basis, attention was turned to the prevention of whooping cough by vaccination. This problem was very much more difficult, partly because immunity to whooping cough appears to be mainly antibacterial, not antitoxic, and partly because whooping cough frequently affects infants at a very early age, before active immunisation can be successfully undertaken. Workers in the Oxford laboratory carried out carefully controlled trials of whooping cough vaccine in residential nurseries, and in children attending infant welfare clinics and day nurseries. The results of this first series of tests were very disappointing, and gave little evidence of protective power in the vaccine. There was no obvious reason why children inoculated in this country should not have benefited from the vaccine when so many favourable reports of whooping cough vaccination had been published in the United States and Canada. The subject is at present being investigated further under the general direction of a Whooping Cough Sub-committee, and it is hoped that the reason for the discrepancy between the English and American results will be discovered.

Water and milk.—Research work, which need not be described in detail, was carried out on the bacteriological control of water and milk supplies, and confirmation obtained of the value of the official tests laid down by the Ministry of Health.

Fungus infections.—As a preliminary to the preparation of a programme of research, the Council's Committee on Medical Mycology (p. 424) recommended that a survey be made to obtain a general indication of the extent, character and gravity of fungous diseases in Great Britain. This survey was undertaken by Dr. J. T. Duncan from the Winchester laboratory during 1944-45. Requests for material from known or suspected mycoses were addressed to members of the E.M.S. Pathological Service and similar organisations: these yielded about 1,500 specimens, some of which, however, were not of mycological interest.

Among the grave systemic mycoses encountered was histoplasmosis—the first case diagnosed in Europe and only the second in the Old World. Later a second case of histoplasmosis, of an unique kind, was identified and a study was made of the fungus *Histoplasma capsulatum* from the two cases, with special regard to the character of dimorphism. Other systemic mycoses encountered were torulosis, of the central nervous system and also in the generalised and subcutaneous forms; chronic sporotrichosis; and many cases of actinomycosis caused by the anaerobic *Actinomyces bovis* Harz, and some by the semi-acid-fast *Nocardia asteroides* group. Mucormycosis, affecting the brain, the lungs and other organs or tissues, was diagnosed in histological preparations from six cases, but from only one case was a culture of the infecting fungus available. The infection seemed usually to be of haematogenous distribution. Many examples of moniliasis were studied, including an unusual case of chronic mycotic glossitis of 21 years' duration in a seaman aged 25. The dermal form of moniliasis, including paronychia, was not uncommon, and an observation was made of the unfavourable effect of local penicillin treatment in a series of cases of otitis media complicated by

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"*Monilia*" infection. The pulmonary disorder known as farmer's or thresher's lung received attention, but a mycological study, except of the sputum, was not feasible. Data bearing on this interesting, supposed mycosis were collected.

It was inevitable that the dermatomycoses should have provided the greater number of specimens, and these revealed an unexpectedly high incidence of *Microsporum canis* (the common parasite of dogs and cats) in tinea capitis of children in the south-western counties. In a number of villages in South Devon *M. canis* var. *felineum* predominated to the apparent exclusion of *Microsporum audouini;* and in Portsmouth, where, despite the reduction of the child population by wartime evacuation, attendances at the ringworm clinic reached the highest number for about 20 years, the only dermatophyte found in the *indigenous* infections was *Microsporum canis* var. *lanosum*. Fifty per cent. of the specimens from tinea capitis in the London area yielded *M. canis* var. *felineum*. There was clear evidence of transmission of the animal *Microsporum* from child to child, but it is probable that the number of transmissions in series is limited and frequent renewal from the animal host is necessary for the continued propagation of the disease on children. In Portsmouth, a history of contact with a presumed infected dog or cat was obtained in about one case in four of the infected children. In the industrial Midlands, on the other hand, the predominating cause of tinea capitis was the common parasite of children, *M. audouini*, and in epidemics of ringworm in South Wales, East Anglia and Hertfordshire this species was the only fungus involved. While infections by the alien *M. canis* are usually much more easily cured than those by *M. audouini*, and may not require X-ray treatment, they introduce a new problem in epidemiology and control.

An investigation of tinea pedis in members of the Fighting Services showed, at first, a relatively high incidence of *Epidermophyton floccosum*, but, later, isolations of *Trichophyton interdigitale* (syn. *T. mentagrophytes*) were markedly increased, and finally, with the inclusion of personnel returned from South-East Asia, a large proportion of the specimens yielded *Trichophyton rubrum*.

From these and other observations it is evident that fungous disease in Great Britain presents a field for further investigation and research.

Publications

A list of publications by members of the Emergency Public Health Laboratory Service and their collaborators, during the period under review, is given on pp. 410-413.

Emergency Register of Pathologists and Laboratory Technicians

Throughout the war the Council advised the Central Medical War Committee on the allocation of pathologists to emergency duties, and the Ministry of Labour and National Service on the recruitment or reservation of laboratory technicians engaged in pathological work. In this task the Council were assisted by a special committee of pathologists set up towards the end of 1938, and later also by consultants in the London Sectors and the various provincial Regions.

It was clear that there would be a great demand for pathologists for the Fighting Services, for the Emergency Medical Services under the Ministry of Health and the Department of Health for Scotland, and for the Emergency Public Health Laboratory Service described above, as well as to some extent for the Emergency Blood Supply Depots. Pathologists would at the same time have to be retained for ordinary public health, hospital and private

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work, for the manufacture of immunological supplies, and for teaching medical students. Those engaged in research were likely to be required for the investigation of special wartime problems.

A similar situation of course existed in the country with regard to medical personnel generally, but it was expected to be particularly acute in the case of pathologists, owing to the small total number available—in many areas there was only a single pathologist. There were other reasons for dealing separately with pathologists, as their professional circumstances are in several respects different from those affecting other kinds of medical work. Pathologists are for the most part not engaged in private practice, and do not become members of the honorary staffs of hospitals; the tendency is for them to hold salaried appointments. Whereas junior men who are aiming at specialisation in clinical branches may be suitably employed in general medical duties, pathologists devote themselves entirely to laboratory work from an early stage; such experience, moreover, may date from before the time of medical qualification, if a scientific qualification has previously been held. It was necessary, also, to consider the use of scientifically trained pathologists (chemical pathologists, and a small number of bacteriologists) who were not members of the medical profession. In addition, the possibility of the enemy resorting to bacteriological warfare meant that pathologists and their skilled assistants might be called upon for work of a special kind.

It was accordingly decided to compile a separate Register of Pathologists, containing fuller particulars of experience than was recorded in the British Medical Association's register of the medical profession as a whole, and differentiating between such branches as clinical pathology, morbid anatomy, bacteriology and biochemistry. Pathologists with other than medical qualifications were included, and a supplementary register of skilled laboratory technicians in this field was also created.

In response to circular letters issued early in 1939, lists of staff were obtained from some 400 laboratories. Question forms were then provided to the appropriate individuals on these lists, and from the information thus received the registers were built up—containing at the outset particulars of about 600 medically qualified pathologists and 170 others, and of about 1,350 skilled laboratory technicians. These numbers were augmented as further information came in or as new personnel was recruited to the subject.

The Register of Pathologists proved of great utility as a source of information on which to advise the Central Medical War Committee about medical workers in this field, and the Ministry of Labour and National Service with regard to pathologists without medical qualifications. It was necessary, however, to go further to ensure that the supply of new recruits to the subject should not cease during the war and the total numbers become quite inadequate. In the first place, it was essential to defer for a time the calling up for military service of young men partly trained in pathology, as this would have involved their allocation to general duties and their consequent loss to the special subject. Later it became necessary to obtain approval to defer a quota of recent graduates as trainees in pathology, and to retain them as assistants in civilian employment until they were sufficiently experienced to take independent charge of laboratories.

The Register of Pathological Laboratory Technicians was equally useful as a basis for action. At an early stage in planning recruitment to the Forces, the Ministry of Labour and National Service agreed to include skilled laboratory assistants in the Schedule of Reserved Occupations. When that system was superseded later in the war, the Ministry delegated to the Council the nomination of those in this category whose recruitment should continue to be deferred, and of those who should be recruited for duty in the Fighting Services in

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their occupational capacity. This arrangement, which persisted until the end of 1946, proved satisfactory and was made possible only by the existence of the Register.

The special committee met mainly in the planning period, and during the war had only to review progress and to consider occasional questions of principle. The day to day handling of the registers and of the correspondence arising was naturally a matter for the Council's office; the latter was much indebted for advice to Dr. (now Sir Philip) Panton, who became chairman of the special committee in 1941 and was throughout the Council's representative on the Central Medical War Committee.

Blood Transfusion

The London Emergency Blood Supply Depots

From the time of the Munich crisis in 1938 the question of blood transfusion during wartime had been much in the minds of medical men. Its limited use during the war of 1914-1919 had indicated its potential value, and the practice of transfusion for peacetime needs had afterwards developed rapidly. The important place of transfusion in the treatment of battle and air-raid casualties was not demonstrated, however, till the Spanish Civil War, when it was clearly shown that the blood transfusion service organised by Dr. F. Duran-Jorda was responsible for saving the lives of many wounded.

Dr. Janet Vaughan, in whose laboratory Dr. Duran-Jorda was working in the months preceding the recent war, took the first step towards the establishment of a large-scale transfusion service for air-raid casualties in this country, by initiating discussion among pathologists of the ten sectors into which the Greater London area was divided in the plans for an Emergency Medical Service. A private meeting was held on 5th April, 1939, at which it was agreed that an organised blood transfusion service for the London area would be essential in the event of war, the majority taking the view that arrangements depending upon individual hospitals would inevitably break down. After this meeting a detailed scheme was drawn up, including possible sites for four central depots, names of individuals suitable as depot directors, and equipment and staff requirements. Within a few days of receiving the memorandum, the Council asked Dr. Vaughan to discuss the proposals with Professor Topley (p. 161), one of their members. An estimate of cost was then prepared, upon the assumption that 10 per cent. of casualties would require transfusion and that each depot must be in a position to supply 500 bottles of group "O" blood a day in an emergency, or an average of 25 bottles of group "O" blood a day, and to hold 500 bottles in cold store. To meet these needs a donor panel of 20,000 donors was considered necessary for each depot area.

On 20th April the proposals, modified to form a single integrated scheme to be centrally administered, were officially adopted. At the same time the four Depot Directors nominated in the scheme (Dr. H. F. Brewer, Dr. M. Maizels, Dr. J. O. Oliver and Dr. Janet Vaughan) were asked at once to perform blood-grouping tests upon 20,000 donors in their respective areas, and to find suitable premises.

The arrangements were pressed forward in close touch with those being made for Army needs by Professor J. Beattie; and liaison officers were appointed to integrate the sector and the depot organisations, under the Emergency Medical Service and the Council respectively. Thus, transfusion equipment and donor enrolment cards were standardised for the whole London area, irrespective of whether depot or sector organisations were concerned. The standard equipment adopted for the purpose included

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the special design of blood bottle now widely known as the M.R.C. transfusion bottle. Donors were enrolled both in the depot areas and by the sector transfusion officers. Efforts were made by the latter to see that each hospital, though entitled to call upon a central depot, had an adequate donor panel of its own and was provided with equipment and facilities for bleeding in case of emergency.

Early in July, 1939, Professor G. Payling Wright, Chairman of the Blood Depots Committee (p. 424), was able to report that certain stocks of equipment were ready for despatch to depots and sector hospital, as a result of orders placed by the Council on behalf of the Ministry of Health. The Depot Directors were, in turn, able to report a satisfactory increase in donor panels, and that necessary alterations and the provision of essential services were being made on the depot premises. Skeleton staffs (medical, technical and clerical) were appointed to take up their duties at the depots immediately a state of emergency should arise. By August the depots had essential equipment available, including large refrigerators for blood storage, and before the end of the month this equipment was installed and in working order. On 1st September telegrams were received from the Council instructing the depots to start bleeding their donors, and on the outbreak of war stocks of blood were available at the four London depots for issue to hospitals. It was gratifying to see how easily the organisation, planned without any practical experience of a large scale transfusion service, swung into action, reflecting great credit on all those who had given so much time and thought to the preparation of the scheme.

Siting of the depots.—As the primary duty of the depots was to supply the needs of the hospitals in the London sectors during air raids, it was necessary to place the depots as near as possible to the main concentration of hospitals and yet outside the central London " target " area. The choice was also controlled to some extent by the premises available. Luton (N.E. London Depot), Maidstone (S.E. London Depot), Sutton (S.W. London Depot), and Slough (N.W. London Depot) were finally selected. At Luton the depot was housed in the disused portion of a hospital. At Maidstone two houses were converted, at Sutton the premises of an adult school were used, and at Slough accommodation was found in the social centre of the Slough Trading Estate.

(Some later developments may be noted. In June, 1940, the Ministry of Health formed a Regional Transfusion Service, and asked that the Sutton and Maidstone Depots should take over the S.E. Region with help from sub-depots at Canterbury and Hastings. Subsequently, owing to the closing of the Oxford Regional centre, the Slough Depot became responsible for an area extending to Reading on the west and to Buckingham on the north. The Luton Depot extended its area to Colchester in the north and, with the help of the transfusion officer in Sectors 1 and 2, took care of Essex to the coast. Thus, the area which, with its associated sub-depots, was looked after by the four London depots eventually extended over the whole south-eastern corner of England, with its inland boundary running roughly from Portsmouth to Buckingham and from there to Colchester.)

The positions of the four depots were also chosen from the point of view of potential donors. Luton is a large industrial town; Maidstone a considerable town in a rural community; Sutton a dormitory area of London; and Slough an important manufacturing centre. As regards donors all proved suitable, especially Slough, where the depot was in the social centre of a large trading estate and donors could be obtained at very short notice to deal with an emergency demand.

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None of the premises occupied was ideal for the purpose, and the Depot Directors had to contend with accommodation which, though adequate for the supplying of relatively fresh whole blood as originally envisaged, proved deficient when the newer, more refined and more difficult techniques were introduced.

Administration.—The central administration by the Council involved some difficulties and called for flexibility and understanding. Firstly, the depots had to develop an entirely new service and to begin operations before a detailed organisation or establishment could be worked out: this led to each Director developing his unit along individual lines. Secondly, although the primary duty of the depots was that of blood supply, they had to undertake concurrent research in a relatively new field: here again the predilections of the individual Directors, or the special problems passed to the respective depots for solution, determined their activities. Thirdly, blood transfusion procedures were continuously changing during the war, due to experience gained and to the progress of research in this country and elsewhere.

The history of the London depots shows that good results were obtained from a flexible scheme and a considerable degree of decentralisation. Indeed, had a rigid organisation been imposed at the outset, the whole scheme would have had to be reconsidered within a few months, owing to the impact of new ideas. If this had been impossible, dynamic developments would have been ruled out and the depots would have been reduced to a static condition as mere suppliers of blood and transfusion equipment; they could never, in that event, have taken advantage of the great opportunities for investigation and experience which were presented by the numbers of the wounded, the self-sacrifice of the donors, the co-operation of hospitals, and the enthusiasm of their own staffs (including many voluntary workers).

The depot system in operation.—For the first nine months of the war there was no air attack on London. These early months were therefore spent in perfecting the arrangements for large-scale bleeding, in improving the equipment, in educating the staffs of casualty-receiving hospitals in transfusion methods, in research, and in keeping up the supply of blood for hospitals in case bombing occurred and for use in their ordinary civilian patients. In this way experience was gained in blood banking and delivery. The donors were bled in rotation and they also gained by the experience. Moreover, the donor panels were increased by further propaganda.

As conditions at first were unexpectedly quiet, the sector blood supply scheme as a whole was never really called into play, the depots being able to provide all the blood that was necessary. In many sectors, therefore, the local schemes fell into disuse and were subsequently absorbed by the depot organisation. In other sectors the local schemes worked simultaneously with the depots from the start and both systems continued to operate in complementary fashion.

It had been thought that under emergency conditions the casualty-receiving hospitals would be so overworked that they would not be able adequately to group all recipients and cross-match their blood with that which would be supplied. It was therefore recommended that the casualties should be given accredited " universal " donor (group " O ") blood. This involved repeated bleeding of a section of the population (the universal donor comprises about 40 per cent. only) and turning away the remainder. Early in 1940, however, the production of liquid serum and plasma was undertaken. Such products could be given to all recipients irrespective of their blood groups, and prepared from blood of all donors. To meet this demand, the depots increased their bleeding programme, issuing the " universal " donor blood for whole blood transfusion and reserving the blood of the donors of other

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groups for the production of plasma or serum. In this way the volunteers of all groups were effectively used. By the autumn of 1940 methods of prolonging the useful life of whole blood had been developed and supplies of liquid serum and plasma were available, so that the actual stocks of transfusion material at any depot were much higher than previously. When the air attacks on London began in the autumn of 1940, co-operation had been so well developed that when casualties were received by hospitals there were few difficulties from the supply point of view. There was a tendency to call for serum and plasma because of their ready availability in emergency, because they were new products, and because their trial in the treatment of "shock" was being widely recommended, but the limited supply restricted their use. Information collected at this time showed that about 10 per cent. of all casualties required transfusion, that each casualty received about one litre of transfusion fluid, and that two bottles of blood were used for every bottle of plasma. Subsequent experience has shown that this proportion is clinically desirable in many types of injury. From these estimates, and from the experiences gained during the air-raids, it was possible for the depots to obtain more definite ideas as to the stocks if was advisable to hold to meet casualty needs.

As is well known, the persistent bombing of London lasted for three months, and for a further three months there was acute but intermittent bombing. Throughout this time the four depots were able not only to supply the needs of the casualty-receiving hospitals for whole blood, but also to bleed in excess of this for the further production of liquid plasma and for the provision of serum to the Serum Drying Unit established by the Council at Cambridge (p. 193), which in 1940 had passed from an experimental stage into relatively large-scale production.

In the period that followed the cessation of major bombing attacks in May 1941, it was expected that the utilisation of whole blood by the hospitals would decline. In practice, however, this did not happen. The value of transfusion, particularly of blood but also of blood products, had been effectively learnt while casualties were numerous, and more doctors had gained experience in the technique of transfusion. Thus, in 1941-42, so far from the demands for whole blood falling off, there was actually a considerable increase. Bleeding was maintained at a high level also to recoup the reserve stocks of plasma and serum which had largely been used up in the period of heavy air-raiding. With the increased bleedings, and the lessened call for blood products when casualties ceased to occur, these stocks were rapidly regained. It was quickly discovered, however, that where consumption did not balance production in the case of liquid plasma and serum, there was considerable wastage due to deterioration by the precipitation of the unstable elements. There was thus a growing need for the preparation of stable dried blood derivatives in place of the unstable liquid products. This demand was met by the establishment at Cambridge in 1942-43 of a much larger drying unit (p. 193), which was capable of dealing with almost all the output of serum and plasma, not only of the London depots but of the rest of the country as well. (In June, 1940, the Ministry of Health had set up a series of blood depots, on similar lines to the London depots, in the following regional centres:—Cambridge, Nottingham, Leeds, Newcastle, Liverpool, Manchester, Birmingham and Oxford: the South-Western Region had been taken over by the Army Blood Supply Depot at the outbreak of war, with its centre at Bristol.) Thus by 1943 adequate reserve stocks of the dried materials had been built up by the London depots, and such surplus material as was produced could be given to the Services and to the Colonies (notably Malta).

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From this time to the end of the war, the depots had sufficient stocks to meet all emergencies. The demands due to the intermittent bombing early in 1944, and to the subsequent flying-bomb and rocket attacks, were all successfully met. It is true that the casualty figures never reached the high levels estimated before the war as likely to occur; but it seems that the organisation would have been capable of meeting these demands, for experience showed that the amount of transfusion material required during the first hours following an air-raid was conditioned not only by the number of casualties but also by the fact that any one hospital could undertake only a certain number of transfusions in an emergency, however many casualties were received. If this demand could be met, the depot had several hours in which to call up donors for bleeding and to collect further material ready for issue.

Apart from their routine duties of supplying blood, blood products and equipment, the depot staffs gave much advice to hospitals on transfusion matters and carried out many *ad hoc* inquiries. They co-operated in work on new blood derivatives, both by supplying the raw material, and by making tests to determine whether the products were suitable for clinical use; such investigations were proceeding almost continuously throughout the war. In addition, the depot staffs accomplished much fundamental research of great value to the development of transfusion practice; the character and volume of their research work are indicated on pp. 188-195 below and by the published papers listed in Appendix C (pp. 406-410).

Transport.—During air-raiding, flexibility in transport was essential. Transport was required for the bleeding teams, for the regular deliveries of blood to the various hospitals, and to meet sudden calls for blood due to any incidents. It was impossible to hold at any hospital a blood bank sufficient to meet the sudden and great demands due to an influx of casualties. The local hospital store could meet only the immediate demand, and the deficiency had to be made good by fresh supplies from a main depot. In theory this arrangement had an aspect of uncertainty, but in practice it proved satisfactory. The depots quickly established close contact with their hospitals and no doubt was left as to what should be done by a hospital in an emergency. Relatively few incidents occurred in which the hospitals did not get an interval between being informed that casualties were to be received and their arrival; in this interval the depot van could be despatched with ample supplies of blood. The deliveries all arrived in time and in many cases before the casualties themselves, a fact which reflected the quality of the drivers employed. Accurate and intimate knowledge of the roads under black-out conditions was essential, but had to be coupled with a willingness to drive while a raid was in actual progress and a determination to get to the hospital at all costs, however difficult the blocking of roads or other circumstances might make the journey. These characteristics were found in the men and women drivers employed by the depots, and only those who have experienced a severe air-raid in a blacked-out city can appreciate these difficulties and assign a proper value to the service given.

Bleeding of donors.—In the early days of the war, the bleeding clinics were established in set places, particularly at the blood depots themselves and at hospitals. The donors were called to these central clinics and responded extremely well. Later on, when more and more people began to take an active part in war-work and had less spare time, it was found that donors could be expected to respond to a call to a bleeding clinic only if they lived or worked in the immediate neighbourhood. It became imperative, therefore, in order to spread the burden of blood giving over as wide a section of the population as possible, to send the bleeding teams to the donors. Each depot, therefore, made arrangements for providing mobile bleeding teams, which used as temporary clinics such buildings as local conditions permitted; many of these were first-aid posts or village and church halls.

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The bleeding teams proved highly successful. Well trained, they kept up a strict standard of aseptic bleeding even under difficult environmental conditions, so that risk of contamination of the blood was reduced to a minimum. Working efficiently, they inspired the donors with confidence and ensured that the bleedings caused little immediate or subsequent discomfort. Well informed on their subject, they could answer questions put to them intelligently, and spread enthusiasm which did much to secure a loyal donor panel. The development of the bleeding team was a most important factor in maintaining a secure supply of blood and blood products of first-rate quality.

Scale of operation.—All the four depots carried out their work on similar lines, bleeding donors at about the same rate and issuing supplies and equipment in corresponding amounts. Complete figures are available for only one depot for the five years from September, 1939, to September, 1944. During this period 128,320 donors were enrolled, 147,777 bleedings were made, 38,263 blood-giving sets supplied, 49,000 bottles of whole blood issued, and 90,181 bottles used for plasma drying. If these figures are multiplied three and a half times, the result gives a fair estimate of the work carried out by the four London depots during this period.

Depot Directors.—Dr. J. O. Oliver was commissioned in the R.A.M.C. in May, 1940, and the direction of the Sutton Depot then passed to Dr. O. M. Solandt: when the latter was appointed by the Council later that year to take charge of their Physiological Laboratory attached to the Armoured Fighting Vehicles School, Lulworth (p. 141), he was succeeded by Dr. J. F. Loutit. Dr. M. Maizels continued as director at Maidstone until the depot there was partially closed at the end of 1944, becoming a sub-depot of Sutton. Dr. Janet Vaughan and Dr. H. F. Brewer remained in charge of the Slough and Luton Depots respectively throughout the war, after which they were succeeded by Dr. J. Shone with a view to the amalgamation of the two depots in new quarters at Barnet.

Blood Transfusion Research

When the London Blood Supply Depots began work at the outbreak of war, many problems immediately arose which called for either applied or fundamental researches. To advise and assist the Council in promoting this work, the Blood Transfusion Research Committee (p. 425) was formed under the chairmanship of Professor Topley, who was succeeded in May, 1940, by Dr. A. N. Drury. In 1940 also, the Blood Depots Committee which had been dealing, under the chairmanship of Professor G. Payling Wright, with the arrangements of the four London Depots, was merged with the Blood Transfusion Research Committee. Owing to the rapid development of transfusion during the war, numerous small subcommittees had to be set up to deal quickly with specific problems; they were largely recruited from the members of the main Committee, with specialists in the various fields in addition.

Whole blood.—Initially, blood banks were composed entirely of group "O" blood (universal donor) collected in a simple sodium citrate solution. The useful life was seven days, and to maintain sufficient stocks of usable blood involved continuous bleeding of donors, and the throwing away of large quantities of blood as it became outdated. An immediate problem was to find methods of lengthening the useful life of whole blood. It was attacked *in vitro* by a study of the physical and chemical changes occurring in the stored blood, and *in vivo* by the study of the survival of the red cells in recipients after transfusion of stored blood. Colonel (later Brigadier Sir Lionel) Whitby and his colleagues (1940) and Dr. Maizels and colleagues (1940-41) made observations using both these methods. Dr. Mollison, Dr. Loutit and

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Miss I. M. Young (1942-43) carried the work further. Early results (Bushby *et al.*, 1940; Dubash *et al.*, 1940) had confirmed that the addition of glucose increased the keeping capacity of stored blood. Subsequent work showed that this addition allowed refrigerated blood to be kept in good condition for 2-3 weeks instead of one week. Later (1943) it was shown that slight acidification of the sodium citrate glucose preservative increased the effective storage life to four weeks. Investigations were undertaken (Maizels, 1943; Loutit, 1945) in an attempt to elucidate some of the factors involved.

As the war proceeded, the practice of group-to-group transfusion was encouraged, and by this means whole blood from other than universal donors was used. In emergency, however, it was not usually feasible to give individual recipients transfusions of blood of the same group as their own, and group "O" blood had to be relied upon. This had been the practice formerly in some countries but was not generally considered to be safe. Experimental work (Aubert *et al.*, 1942) confirmed that there were protective factors in the human body which largely neutralised the maleficent action of the antibodies of the group "O" plasma. During the whole course of the war remarkably few haemolytic transfusion reactions could be attributed to this cause.

The policy of using universal donor blood almost exclusively for whole blood transfusion, in the circumstances then prevailing, simplified the plasma production plan, as the other groups of blood could be used for making plasma and serum. Blood donors of all blood groups thus became of equal value and the burden of blood donation was spread more evenly over the volunteers.

The discovery in 1940 that the useful life of blood could be prolonged made stored blood more readily available, but the idea of using such blood was not readily received by the clinicians, it being held by many that fresh blood was better. An investigation was therefore instituted to assess the relative merits of fresh and stored blood. The four London Blood Supply Depots undertook this work in co-operation. Their conclusions rapidly reached (Brewer *et al.*, 1940) were that in the treatment of acute haemorrhage stored blood was as good as fresh blood, though mild reactions seemed to be more frequent after stored blood transfusion. For non-acute haemorrhage and the restoration of red blood cells it seemed obvious that the stored blood would be less effective than fresh blood, but with the improvement effected in the keeping qualities, blood stored for several weeks is now known to be but little inferior to fresh blood.

Blood-grouping.—The collection and use of whole blood called for precise methods of blood-grouping and for large amounts of high quality grouping sera to carry out the tests. Some months before the war began the Council had accordingly assigned the task of providing serum to the Unit (administered by them on behalf of the Rockefeller Foundation) working under the direction of Professor R. A. Fisher in the Galton Laboratory, University College, London. On the outbreak of war, this Unit moved to Cambridge. At first, undergraduates and residents were able to provide adequate quantities of blood, but as requests for grouping sera increased a wider net had to be drawn. A convenient source proved to be an intake Depot of the Royal Air Force, where the medical officers and orderlies co-operated by taking samples of blood, usually about one thousand a week. The group of each blood was determined at Cambridge and the serum further tested for suitability as a grouping reagent. The blood groups were reported and stamped on the identity discs of the airmen. Those whose serum was selected for blood grouping were asked to give blood, and many hundred pints were collected in this manner. In the end nearly 200,000 airmen had been accurately grouped, the results incidentally yielding very reliable figures for the average blood group distribution in the United Kingdom. For the last two years of the war the Transfusion Services were the main source of supply, and

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collaboration with a large blood collecting centre proved to be far the most satisfactory method of obtaining grouping serum, permitting large stores to be acquired in a short time.

The publication in the U.S.A. in 1940 of the discovery of the Rh factor—the blood group factor other than the A and B factors which had to be taken into account in blood transfusion practice—was quickly followed up. At the request of the Committee, Dr. G. L. Taylor and Dr. P. L. Mollison wrote a joint letter to the *Lancet* and *British Medical Journal*, asking to be put in touch with obstetric patients who had been delivered of infants affected with *erythroblastosis foetalis* (haemolytic disease of the new-born). The medical profession responded admirably, and in a short time many sera had been tested and the active ones used as reagents in conjunction with animal sera prepared in this country and the U.S.A. Although full information about the importance of the Rh factor did not reach this country till the end of 1941, within a year the American work had been confirmed and additional findings had been recorded (Boorman *et al.*, 1942; Taylor *et al.*, 1942). In the subsequent years a remarkable advance was made, notably by the Galton Serum Unit (Dr. G. L. Taylor, Dr. R. R. Race and their colleagues), and a whole series of Rh factors has been described and their inter-relationship determined.

Seven " allelomorphs " of the Rh gene have been isolated, six of which were isolated independently at about the same time in America. An " incomplete ", non-agglutinating, form of anti-Rh has been discovered, which is as dangerous in causing haemolytic disease as is the " complete " agglutinin. This also was described simultaneously in America. Early in 1944 the results were studied by Professor R. A. Fisher, who proposed the theory, which has now received considerable support, that three closely linked loci, each with at least two allelomorphs, were responsible for the Rh groups. The theory demanded one more gene combination and two more antibodies.

The Transfusion Services received invaluable help and advice from the late Dr. G. L. Taylor and his Unit. Methods suitable for large-scale blood grouping were instituted on lines which would exclude, so far as was humanly possible, either technical or clerical errors. These methods were published (Taylor *et al.*, 1942), and were subsequently described in more detail in a pamphlet, " The Determination of Blood Groups ", which was issued in 1943 as *M.R.C. War Memorandum* No. 9. The same memorandum also included instructions for Rh blood grouping. On the basis of these recommendations, blood grouping of bottles of stored blood can be done very accurately, and there has in fact been a truly remarkable freedom from incompatible transfusion reactions due to wrong grouping of the donor blood.

Donors.—It was to be expected that when volunteers were venesected by the thousand, some ill-effects would be reported. A special survey was accordingly made to determine the immediate ill-effects, chiefly fainting attacks, and the remote effects, good or bad, resulting from blood donation. A report was submitted which has since been published (*Brit. med. J.*, 1944, **i**, 279). It was concluded that, apart from the advisability of excluding donors who gave a history of fainting either associated or unassociated with blood donation, no factor open to correction was involved. Delayed fainting or faintness occurred in 1.2 per cent. of men and 1.8 per cent. of women donors. As against 14 per cent. of donors who experienced some discomfort, however small, 10 per cent. felt especially fit after the operation.

Recipients.—The Committee watched with some anxiety for accidents or deaths in recipients following transfusion, a not unlikely event when large numbers of badly injured patients were being given massive transfusions under emergency conditions. An effort was made early in 1940 to

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collect reports of any such accidents or deaths occurring in the London area. The analysis of the small number of reports received indicated that very few of the accidents and none of the deaths reported could be attributed to the transfusion. On the other hand, two instances of death following transfusion came to the notice of the Committee from other sources. In both cases it was associated with the giving of blood containing a diphtheroid organism which grew at temperatures as low as +2°C, and might have been due to inadequate sterilisation of the transfusion equipment. These events led the Committee to stress the paramount importance of ensuring the proper functioning of the autoclaves in use; a special article on the subject by Dr. E. T. C. Spooner and Mr. L. H. Turnbull, from the Slough Depot, was published in the *Bulletin of War Medicine*, 1942, **2**, 345.

Apart from the rare accidents following transfusion, it was common to observe reactions characterised by evanescent rigors and rise of temperature after the giving of blood, plasma or serum. This problem was constantly before the Committee. Every effort was made to eliminate such reactions by the careful preparation of all equipment and transfusion material; yet, though their incidence fell, they still occurred. Many attempts, both clinical and experimental, were made to elucidate the nature of these reactions, and the Committee finally decided that the only hopeful approach was to prepare special batches of material from the pooled serum or plasma of a very large number of donors, and to issue this in bottles all containing identical material, to special investigators working to exactly the same standards. This plan was nearly in operation when serious doubt arose as to the advisability of using material prepared from a large number of donors, owing to the risk of homologous serum jaundice (see below). At about the same time, the war ended, there was a rapid redistribution of hospital personnel, and the investigation was abandoned.

Transmission of disease by transfusion.—The ill-effects discussed above were those following closely upon transfusion, but the possibility of disease being conveyed to the recipient and developing after an interval had also to be considered. In 1937 an event had occurred in which several deaths due to acute hepatic necrosis followed the giving of adult human serum for the prophylaxis of measles. The Committee, therefore, had it in mind from the very beginning, that the use of human serum and plasma for transfusion might occasionally be followed by jaundice or acute hepatic necrosis.

The Committee repeatedly brought the possible risk of post-transfusion jaundice before those responsible for transfusion; but it was not until 1942 that concrete evidence of the occurrence of post-transfusion jaundice was obtained, when out of a series of patients who had received serum for transfusion several developed jaundice some 50-60 days later. About the same time additional evidence of its occurrence was obtained in a series of cases transfused with bottles of serum from the same batch. In those days it was the custom, in order to decrease the losses due to filtration, to pool the serum and plasma from the blood of 500-1,000 donors, and it was thus possible for a single donor to infect a large number of bottles.

Although workers with much experience of transfusion felt that jaundice as a complication must be rare, a follow-up of cases transfused with plasma or serum was instituted. In the selected area, it was found that jaundice occurred in 7-10 per cent. of those transfused with filtered serum or plasma. The reason why it had been missed was that the disease was in the vast majority of cases, very mild, and no deaths had occurred. In another area almost identical results were obtained. On the other hand, in a follow-up of 1,000 cases receiving only whole blood (3,800 bottles) the incidence was less than 1 per cent., suggesting that the donors responsible must be relatively

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uncommon. This was supported by work in which samples of fresh serum from 10 different donors were injected into a similar number of recipients without jaundice occurring. Analysis by the Ministry of Health of the records of Service patients treated in E.M.S. hospitals for wounds and other conditions showed, nevertheless, that the incidence of jaundice was much higher in those who had received transfusion than in those who had not, and that the small number of fatal cases of jaundice among the patients all occurred in the former group. In interpreting these results, it had to be remembered that in addition to receiving transfusion, many wounded men were given other remedies by injection, and the risk of the transmission of jaundice by this means was not negligible.

Administrative action on two lines was taken, namely to reduce the number of donors contributing to a plasma or serum pool to 10 as a maximum, and to emphasise that plasma or serum should be used only in cases in which, owing to urgency, whole blood could not be used. Follow-up investigations have since been undertaken upon the incidence of jaundice in cases receiving plasma or serum from these small pools. The problem was also considered by the Jaundice Committee appointed by the Council, which organised extensive investigations of infective hepatitis and homologous serum jaundice, including the jaundice following transfusion, as described on pp. 66-8 and 175. Apart from jaundice, there was no instance of the transmission of any other disease by transfusion.

Liquid plasma and serum.—In December, 1939, information was received from the U.S.A. that unfiltered liquid plasma was a useful substitute for whole blood, but serious doubts were expressed as to the advisability of issuing unfiltered plasma, the opalescence of which prevented the detection of contamination by visual inspection. Although much unfiltered plasma was used successfully at the time of the Dunkirk emergency, it was decided thereafter that no product should be issued for transfusion which had not been bacteriologically filtered. Plasma cannot thus be filtered, as clotting occurs in the pads, so attention was directed to serum, which can be readily filtered and gives a clear resultant fluid. The use of serum, however, called for special bleeding, and there was still the plasma from time-expired blood running to waste. Various methods of overcoming the filtration difficulty with plasma were tried; they included recalcification and the addition of serum (Maizels, 1941), altering the *p*H to 10.6 (Army Blood Transfusion Service, 1942), preliminary absorption of the fibrinogen by kaolin (Maizels, 1944). An entirely different approach was made by precipitating the fibrinogen with ether, after which filtration was possible and a crystal clear product was obtained (McFarlane: *Nature, Lond.*, 1942, **149**, 439; Kekwick, Mackay and Record: *Ibid.*, 1946, **157**, 629).

Although the detection of gross contamination in liquid filtered blood products was simple, they had the property, even if sterile, of forming small clots and of developing deposits of a lipo-protein nature, the appearance of which could not be readily distinguished from that of mild contamination. Modifications of the ether process were introduced late in the war, by which all traces of fibrinogen were removed by the addition of human thrombin. By this means a more stable liquid product has been obtained, but it is still too early to state that it is completely stable. Although the work on the preparation of a stable liquid product has not been completed, the developments were of the greatest importance in supplying the very large amounts of plasma and serum required for the drying plants.

Dried blood products.—Although it clearly was impossible to dry whole blood without destroying the red cells, the proved clinical value of plasma and serum gave great impetus to providing these in a dry form. Such products

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would be stable at all temperatures, capable of being transported to all parts of the world without deterioration, and readily reconstituted for transfusion.

A method of condensation drying of proteins had been worked out by Dr. R. I. N. Greaves and his colleagues in the Department of Pathology at Cambridge some years before the war, and the Council had arranged for investigations to be carried out there on the preservation by drying of the large amounts of tetanus antitoxin which were acquired against a possible emergency. The results indicated that such drying had no deleterious effects on the product. From these experiments a drying plant was designed for dealing with large quantities of tetanus antitoxin. At the outbreak of war the Council proceeded with the erection of drying plants on a similar plan for the drying of blood serum and plasma for transfusion, and, as a consequence, the Cambridge Drying Unit was established under Dr. Greaves's direction. The original plants were able to dry 84 litres of serum per week, the liquid material being provided by the London Blood Supply Depots, and the filtration of this material being undertaken at a special Filtration Unit started in the Department of Zoology, Cambridge.

From March, 1940, to June, 1941, the Serum Drying Unit dealt with 18,767 bottles of serum, each containing 200 ml. The majority of this dried material went to the three Services, the remainder to the London area. Amongst the other materials dried experimentally were cat, dog, and goat serum and plasma for various workers experimenting on shock in animals. Smaller quantities were dried, during this period, of human blood-grouping serum, measles convalescent serum, ether extracted serum, haemoglobin solutions, pregnancy mare serum, foot-and-mouth disease vaccine and therapeutic antisera.

In June, 1941, a change was made to drying 400 ml. amounts in the standard M.R.C. transfusion bottle, following the introduction of high speed vertical spin-freezing by the Unit, and within the next eighteen months over 30,000 bottles of serum were dried in this way for the Royal Navy. In June, 1942, work was started on a much larger drying plant, as the result of a generous gift to the Council from the Wellcome Trustees. This plant came into operation on the 1st February, 1943, and between that date and September, 1945, when it was closed down, it had dried close on a half million bottles of plasma and serum. The output of this large plant supplied within that time the total requirements of the Royal Navy and the civilian population, a proportion of the Army needs, and the home needs of the R.A.F.

During the early war period, technical advice and assistance were given by the Unit in the design of drying plants for the Wellcome Physiological Research Laboratories, the Army Transfusion Service and the Scottish Transfusion Service; in the later war period, advice was chiefly sought for the design of drying plants for penicillin production. A full account of the work of this Unit will be found in the Council's *Special Report Series*, No. 258.

Sterility of whole blood and of blood products.—The maintenance of the sterility of blood and blood products is a source of anxiety to a transfusion service, and much work was undertaken on this problem. A series of tests was made to ascertain the incidence of infection when using the bleeding technique adopted. It was found that in some 2 per cent. of donations the blood obtained showed bacterial contamination as it entered the bottle, probably from bacteria lying in the deeper layers of the donor's skin, though in how many of these instances the blood might have become sterile later by the action of antibacterial substances present in it was not determined. Any method of sampling the actual bottles of blood for bacterial contamination was held to be undesirable. It was therefore decided that no routine tests could be made for the sterility of blood, but that rigid adherence to an aseptic

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bleeding procedure, and the bleeding of donors by teams specially trained, were the best means of minimising the risk of bacterial infection. These procedures proved very satisfactory in large-scale practice, although one or two deaths which could be attributed to the giving of infected blood have occurred.

The preparation of large quantities of blood products, which are in themselves excellent culture media for bacteria, raised technical difficulties of some magnitude. The margin of safety would have been considerably increased if a suitable antiseptic could have been added. Antiseptics such as "Merthiolate," phenyl mercuric nitrate, the sulphonamides, acriflavine, etc., were investigated from this point of view by Miss M. E. Mackay. All failed to satisfy the exacting requirements, either because the introduction of large quantities of antiseptics in massive transfusions was clinically undesirable, because they failed to kill all the possible contaminating bacteria, or because their action did not persist over the long periods of time during which the liquid products were stored. Efforts had therefore to be directed towards the development of techniques to avoid bacterial contamination. The regular testing of the product at various stages in its preparation, and the strict precaution of keeping the fluid product in its final container for 7 days in the incubator at 37° C. and for 14 days at room temperature before issue, which was adopted as a routine procedure, ensured that no product was released which had been infected at any stage in its preparation. When the material was to be dried, it was insisted that this should be carried out in the final container, so as to minimise the risk of infection.

Fibrinogen, thrombin and fibrin foam.—The preparation of fibrinogen, thrombin and fibrin foam from human plasma by Dr. Cohn and his colleagues in the United States made available haemostatic materials which were of much practical value in neurosurgery. A supply of these products was generously provided by the American authorities for trial by British Service and civilian surgeons. The Committee considered the possibility of preparing similar blood derivatives in Britain, but it was clear that it would not be practicable to obtain the elaborate equipment necessary for the Cohn process during the war. The importance of such materials was, however, stressed to research workers, with the result that early in 1944 the ether precipitation method mentioned on p. 192 was successfully modified so that these materials could be obtained by means of simple laboratory apparatus, with yields so high that the process could easily be adapted to production on a larger scale. This was undertaken at the Lister Institute, and in 1945 the substances were issued to surgeons. The supply has been continued, and surgeons are now unwilling to undertake certain operations unless these materials are at hand.

Adult measles serum and globulin.—Under the abnormal conditions of wartime the possibility of widespread epidemics of measles in children gave rise to special anxiety. The Blood Transfusion Research Committee was therefore asked if it could help in the preparation of large quantities of human serum for the prophylaxis of this disease. The Committee had already successfully investigated the possibility of preparing filtered serum in large amounts, and the only difficulty that remained was to obtain the human blood. It was decided to issue an appeal for donors, especially for the preparation of adult measles serum, and to emphasise that donors of other than the universal donor group could be used. The appeal met with complete success, and in February, 1940, the Committee was able to report that some 6,000 doses of the serum were available.

In addition to adult measles serum, the Committee had always in mind the preparation of the immune globulin for the same purpose which was being

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prepared by Dr. Cohn in the U.S.A. and samples of which had been successfully used in this country. In 1945 the ether precipitation method (see above) was further modified and the preparation of immune globulin undertaken. The pilot experiments indicated that the method would prove successful, but owing to the pressure of work more essential to the war effort its development was postponed till after the end of hostilities.

All through the war, the Committee had constantly in view the improvement and standardisation of transfusion equipment, and the potentialities and limitations of artificial blood substitutes such as pectin, isinglass, and periston (of enemy origin), as well as many other matters; none of these artificial blood substitutes was held to compete in practical value with plasma and serum. The Committee contributed appendices on transfusion methods to the two editions of *M.R.C. War Memorandum* No. 1 on the treatment of wound " shock ". The success of the Committee's work was due largely to the fact that the members were nearly all actively engaged in blood transfusion, and to their spirit of enterprise and co-operation.

A list of papers published by members of the staffs of the London Blood Supply Depots and the Galton Blood Grouping Unit at Cambridge, is given in Appendix C on pp. 406-410. Publications from the Serum Drying Unit at Cambridge are listed on p. 343.

IX

MISCELLANEOUS RESEARCH AND OTHER ACTIVITIES SUPPORTED OR ASSISTED BY THE COUNCIL DURING THE WAR

The Control of Cross-Infection in Hospitals

The risks of " hospital cross-infection " in open wounds and burns, and the investigations aimed at its prevention, have been discussed in Section II above and are further considered on pp. 266-272. The danger of the transfer of infection from patient to patient in hospital applies not only, however, to the injured; it is, indeed, much wider in scope, and is an especially serious hazard in children's hospitals, obstetric wards, and hospitals for the treatment of infectious diseases.

Studies in the causes and prevention of hospital infection in general had been promoted by the Council before the war, and in 1939 the Council's Committee on Preventive Medicine set up a special sub-committee (p. 426), under the chairmanship of Dr. E. H. R. Harries, to examine the problem in its various aspects, and to make practical recommendations. These recommendations, which had of necessity at the time to be limited to measures capable of adoption under war conditions, were incorporated in a pamphlet, " The Control of Cross Infection in Hospitals ", published in 1944 as *M.R.C. War Memorandum* No. 11. The Memorandum lays particular stress on the nursing care of young children, since this group of patients is exposed to the greatest risk and suffers the most serious consequences of cross-infection; accounts are given of the prevalence and consequences of cross-infection of different types, the sources and modes of its spread, its prevention and control, and the procedures to be adopted following the occurrence of infection. In seven appendices the Memorandum gives detailed information regarding disinfection and sterilisation, isolation nursing, special precautions for maternity units, the technique of surgical dressings in wards, the application of dust-laying oils to floors and bedclothes, a suggested practical course in bacteriology for nurses, and a list of references to original papers.

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The programme of research work on the control of cross-infection in hospitals is being continued. It has throughout been closely related to the work on air purification (air hygiene) by Dr. R. B. Bourdillon and others, which has been mentioned earlier in this Report (pp. 38 and 46), and is discussed more fully on pp. 213-5.

A potential source of many different types of cross-infection from patient to patient is the use of imperfectly sterilised syringes to give injections; it is a danger of which the magnitude is probably still not fully realised in hospitals and clinics, and by individual doctors, and there is no doubt that it played a part in determining the spread of jaundice (p. 67) and other diseases during the war. To combat it, the Council set up a special committee (p. 426), under the chairmanship of Professor G. S. Wilson, which produced a pamphlet entitled " The Sterilisation, Use and Care of Syringes ", published in 1945 as *M.R.C. War Memorandum* No. 15. The recommendations in this pamphlet, if generally adopted, should do much to eliminate a hazard which is apt to be particularly serious in clinics where large numbers of injections are given.

Classification of Diseases and Injuries

In January, 1942, the Council were asked by the Ministry of Health to advise on a system for collecting and recording statistics of patients admitted to hospital, using a standardised classification of diseases and injuries. The Council accepted this responsibility and appointed a Committee on Hospital Morbidity Statistics (p. 426) to consider means for making the scheme effective. Invitations to nominate representatives on the Committee were sent to the General Register Office, the Ministry of Health, the Department of Health for Scotland, the Ministry of Home Affairs of Northern Ireland, the Medical Departments of the Navy, Army and Air Force, the Medical Services Division of the Ministry of Pensions, the Royal College of Physicians of London, the Royal College of Surgeons of England, and the Nuffield Provincial Hospitals Trust.

The immediate reason for the request from the Ministry of Health had reference to the preparation of the Official Medical History of the War. The Editorial Board of the Medical History had decided that the classifications used for the medical statistics in the Medical History of the War of 1914-18 were not altogether suited to present conditions, and that it was very desirable that close comparability should be achieved between the morbidity statistics of the three Fighting Services, the Emergency Medical Services and the Ministry of Pensions. A further and more far-reaching implication of the proposal was that the new classification, if it proved satisfactory in practice, might be adopted as the standard for national records of morbidity in the post-war hospital services.

Before the Committee was appointed, the Nuffield Provincial Hospitals Trust had had under consideration the question of sponsoring a uniform classification of diseases which might be used throughout hospitals in Britain, and a draft classification had, in fact, been prepared for the Trust by Dr. Percy Stocks and Dr. A. H. T. Robb-Smith, both of whom were members of the Council's Committee, the latter acting as Secretary. Their draft, which adhered closely to the arrangement of the International List of Causes of Death and was similar to the Diagnosis Code of the United States Public Health Service, was considered likely to prove useful both for the immediate purposes of the compilers of the Official Medical History of the War and as a working basis for the fuller classification which the Council's Committee had been asked to prepare. The Committee proceeded to revise and amplify the draft classification, seeking the advice of specialist

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bodies whenever it was considered expedient. Grateful acknowledgment is made of the co-operation received in this way from the Radium Commission, the Joint Tuberculosis Council and the Royal Society for the Prevention of Accidents, as well as from many individual experts.

The revised and amplified classification was issued by the Council in 1944 as their *Special Report Series* No. 248. It was conceived as a provisional classification, which might well require modification in detail, in the light of practical experience of its use. In addition to the tabulation and coding of diseases and injuries, it included a classification of therapeutic procedures (mainly surgical operations) based upon the Standard Nomenclature of Operations prepared for the American Medical Association; it also included a classification of occupations, derived from the Registrar-General's classification at the 1931 census of England and Wales.

The provisional classification has on the whole been well received. It is comparable with the Diagnosis Codes used by the medical departments of the three Fighting Services; it has been adopted by the Ministry of Health for the Emergency Medical Service records, and is being used by the Ministry of Pensions. It has also been adopted by the Regional Bureaux of Health and Sickness Records, established by the Nuffield Provincial Hospitals Trust; by the Radium Commission, the Middlesex County Council, and a number of hospitals and public health authorities throughout the country.

The health and morbidity surveys published in the *Monthly Bulletin of the Ministry of Health and the Emergency Public Health Laboratory Service* (p. 200) have been based on this classification, and in general it has proved a serviceable index of morbidity in various surveys of " hospital " and " ambulatory " sickness, and should form a sound basis for any national classification of hospital and sickness records. It is realised, however, that there would be obvious advantages in achieving not only comparability but identity between the codes used for classifying morbidity and mortality, respectively, and recently the U.S. Government set up a Sub-Committee on classification of diseases, injuries and causes of death, meetings of which were attended in America, in 1945-46, by Dr. Stocks and Dr. Robb-Smith as consultants. As a result, it was found possible to prepare a classification which could combine these two functions, and should have the added advantage of securing uniformity between British and American coding systems. It is proposed that, when this classification has been tested in practice, it shall be submitted to the International body concerned with the revision of the International List of Causes of Death. The new classification is very similar to the provisional classification prepared by the Council's Committee, and where the latter has been modified it is the opinion of the consultants that the alterations are for the better.

Radium and Radon in the War Years

The danger of a wide dispersal of radio-active substances following atomic bomb explosions is now well known. Long before the war, however, it was realised that radium when scattered in the form of a fine dust is a deadly inhalant, and that the risks of its dispersal by high explosive action would be very great unless strict precautions were taken to keep it out of range of enemy air attack. Following consultations between representatives of various bodies concerned with the use and custody of radium, including the Council, arrangements had been made before September, 1939, for boreholes to be constructed at a number of centres in London and other parts of the country, into which radium in suitable containers could be lowered to the safe depth of 50 feet.

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The adoption of this measure for the public safety, from the outbreak of hostilities, had the inevitable disadvantage of depriving many patients with cancer of the benefits of radium treatment, and of interfering with the progress of research in radiotherapy, with which the Council themselves were largely concerned. An earlier development of radiotherapeutic technique—namely, the use of radon gas as an alternative to radium itself—here stood the nation in good stead. For many years before the war the Council and the British Empire Cancer Campaign had maintained a plant for the production of radon, primarily for research purposes, at the Middlesex Hospital, under the direction of Professor Sidney Russ. Another radon plant had been established by the London Hospital, and there were similar plants elsewhere in Britain. For the production of radon it is necessary to keep a large quantity of radium element in solution, and this constituted a special hazard under war conditions. Accordingly, in the summer of 1939 the Council's radon plant was moved to a place of safety in deep caves at Barton-in-the-Clay in Bedfordshire, and accommodation at the same place was provided for the London Hospital radon plant and staff; subsequently, the London Hospital radon plant was taken over by the Radium Commission, who asked the Council to assume responsibility for running it. The amount of Government radium originally allocated by the Council for the production of radon was supplemented by loans of National radium from the Radium Commission, and agreement was reached with that body as to the conditions under which radon should be supplied from the Barton centres to hospitals, so as to ensure its proper and effective use in treatment.

With the continuance of enemy air bombardment of British cities, the facilities for using radium itself in treatment became progressively more restricted, and the demand for radon supplies, as a less dangerous substitute, became correspondingly greater. This need was met by the establishment of a third radon centre at Barton—the Hospitals Radon Centre. Radium for this centre was lent by the Radium Commission and by St. Bartholomew's Hospital, London, and the cost of its staffing and maintenance during the war was provided from generous grants made to the British Hospitals Association for the purpose by the British War Relief Society, Inc., of New York; the task of administering the new centre was delegated by the Association to the Middlesex Hospital, and was later taken over by the Council.

Thus, eventually there were three radon plants at Barton, all under the general direction of Professor Russ, acting on behalf of the Council; between them, over a period of six years, these plants dealt with about 9,500 requisitions for radon for use in treatment or research. Most of the requisitions were made for the treatment of patients with cancer, and it is certain that had the radon supplies not been available, the great majority of these patients would have been deprived of radiotherapy under war conditions.

The methods of treatment with radon have some technical advantages over the use of radium for certain purposes, but the preparation of radon sources remains a costly and dangerous process. The Council are glad to note that Government action is now being taken to concentrate the production of radon at a specially equipped National centre, which shall serve not only medical but also industrial needs; when that proposal is implemented, their responsibility in regard to the production and issue of radon will be at an end.

The work, during the war years, of the Council's Radiotherapeutic Research Unit, and the studies of the biological effects of radiation by Dr. F. G. Spear, of the Council's staff and his colleagues, are noticed on pp. 272 and 334, respectively.

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Birth Rate and Trends of Population

In relation to the work of the Royal Commission on Population, the Council, in 1944, appointed a Committee under the chairmanship of Sir Joseph Barcroft to consider problems of the physiological aspects of human fertility, referred by the Royal Commission to the Council for advice. The composition of the Committee is given on p. 427. A co-ordinated programme of experimental research under its direction was initiated during the latter part of the war period.

X

WAR PUBLICATIONS

During the war period the issue of the Council's Annual Reports was suspended, as already indicated on p. 13, and, apart from a few numbers dealing with pre-war studies, which appeared in 1939-40, the scope of the monographs published in the Council's *Special Report Series* was restricted to subjects having a direct bearing on the war effort.

Five new series of publications, however, were issued by the Council during the war, to meet emergency needs. The first was the set of seventeen *War Memoranda*, to the individual numbers of which reference has been made in the preceding sections. While most of these included the results of *ad hoc* researches, their chief functions were to present a concise survey of current knowledge of subjects of urgent practial importance under war conditions, and, in many instances, to convey authoritative recommendations by expert Committees for the guidance of those responsible for the treatment of the sick and wounded. Since these memoranda were thus primarily intended for medical officers in the Fighting Services and the civilian Emergency Medical Services, it was clearly desirable that the recommendations should be unanimously endorsed by the various government departments concerned. To ensure this, an Inter-Services Medical Editorial Committee (p. 428), including nominees of the three Fighting Services, the Ministry of Health, the Department of Health for Scotland, the Ministry of Home Security and the Ministry of Pensions, was appointed in 1940, with Sir Edward Mellanby, the Council's Secretary, as Chairman. The Committee met only three times, since it was found that its business could be effectively transacted by the circulation of proofs to members for their comments and suggestions. There is no doubt that this arrangement fulfilled several very useful functions: in addition to providing a wide range of expert opinion and constructive suggestion upon the contents of the memoranda before publication, it had the desired effect of eliminating the risk of the issue of conflicting instructions by different Departments upon the same subject, and it enabled the Medical Directors-General of the Fighting Services and Emergency Medical Services to state in advance how many copies of a forthcoming memorandum they would require for distribution to their medical officers; this information, conveyed to H.M. Stationery Office, assisted that Department to decide how many copies to print for the first issue—an important consideration at a time when paper was scarce.

Apart from extensive official distributions through British, Dominion and Allied government bodies, nearly all the *War Memoranda* have had very large sales, and there is good evidence that the series has been warmly welcomed by research workers and medical practitioners, both in this country

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and abroad. Most of the memoranda have required frequent reprinting, and of some—such as that on the medical use of sulphonamides—a second edition has been necessary to keep pace with the rapid growth of knowledge. In the light of the reception given to this series, the Council propose to issue similar memoranda from time to time under peace conditions, as material suitable for publication in that form—such as authoritative reviews of existing information on important practical problems—becomes available.

The second and third series of special war publications issued by the Council both related to the work of the Industrial Health Research Board and have been briefly mentioned in Section VII above. One of them was a set of five *Emergency Reports* of the Board, which, similarly to the more comprehensive series of *War Memoranda,* give technical summaries of current knowledge or the results of certain *ad hoc* researches made during the war; the other was complementary to the more technical reports of the Board, and consisted of three pamphlets written in relatively "popular" language, and freely illustrated, which were intended to convey the practical results of some of the Board's researches in environmental physiology and industrial psychology to a wider public, especially in industry; these dealt respectively with questions of heating, ventilation and industrial lighting, with the general problems of absence from work and the prevention of fatigue, and with the special problem of sickness absence among women in industry.

The fourth of the Council's series of war publications was the *Bulletin of War Medicine,* issued in six volumes including, in all, sixty numbers. The production of this *Bulletin* was a formidable task, which could hardly have been undertaken by the Council's small headquarters staff without the generous co-operation and assistance of the Bureau of Hygiene and Tropical Diseases, as described below.

The fifth series of publications started by the Council during the war period differs from the others listed above in that it has not hitherto been placed on sale, and has latterly been issued as a joint responsibility of the Council and the Ministry of Health. It consists of the *Monthly Bulletin of the Emergency Public Health Laboratory Service* (p. 164), which is now combined with a *Monthly Bulletin of the Ministry of Health.* Though not available for purchase, it has had a wide distribution to Local Authorities, Medical Officers of Health, bacteriologists and other interested workers, which is still being continued.

A complete list of the Council's Reports, Memoranda and pamphlets published and placed on sale during the years 1939-1947, including those issued on behalf of the Industrial Health Research Board during that period, is given in Appendix A (p. 403). The results of much of the research supported by the Council was published during the war years, as always, in the form of papers in scientific journals, references to which are given in the later sections of this Report; in most cases these lists of references are restricted to papers published before the end of September, 1945, but a few references to later papers describing work reviewed in the text are included. A list of reports and memoranda sponsored by some of the Council's expert Committees, which were published in journals, is given on pp. 405-6; some of these record studies which, although undertaken by their authors for a particular Committee, and reported to the Committee in advance of publication, did not require the Council's financial support; the Council are glad to express their gratitude for such voluntary co-operation to the authors concerned.

A substantial part of the research carried out for the wartime Committees could not, for security reasons, be published before the end of hostilities, but was reported under varying degrees of secrecy to interested workers in Great Britain, the Dominions, the United States and other Allied countries, who

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reciprocated, through their appropriate organisations, by supplying similar unpublished reports upon their own activities; in regard to this exchange of " secret ", " confidential " and " restricted " documents, the liaison between the Council and the Committee on Medical Research of the Office of Scientific Research and Development, Washington, was particularly close and effective; similar liaison was maintained throughout the war with the National Research Council of Canada, and with the Service Departments of each of the Dominions, as well as those of the United States. Most of the reports of the Personnel Research Committees (pp. 132-152) were circulated under conditions of secrecy during the war years, but it is hoped that papers on all the results of major scientific interest will gradually be published as opportunity offers.

Bulletin of War Medicine

Full accounts of the history, functions and production of the *Bulletin of War Medicine* have been given in the final number (Vol. VI, No. 12), published in August, 1946, and need not be repeated in detail here. The Council welcome this opportunity, however, of again expressing their warm thanks to the Honorary Managing Committee and the staff of the Bureau of Hygiene and Tropical Diseases for their indispensable co-operation in regard to the preparation of the Bulletin, as well as to the many experts in different branches of medical science who provided the critical abstracts and review articles of which the Bulletin was composed. They are especially grateful to Sir H. Harold Scott, who originally suggested the co-operative arrangement under which the Bulletin was produced, and was largely responsible for framing its policy; to Dr. Charles Wilcocks, his successor as Director of the Bureau, who, among many other editorial duties, bore the brunt of the task of selecting papers suitable for abstraction; to Dr. J. F. Corson, the Acting Assistant Director of the Bureau during much of the war period, who shared substantially in the detailed editorial work; and to Captain R. L. Sheppard, the Secretary of the Bureau, who supervised many details of printing and production, as well as co-ordinating the manifold duties in relation to the Bulletin voluntarily undertaken by the various members of the Bureau's staff. The production and editing of the Bulletin was, in effect, a joint responsibility of the staff of the Bureau and Dr. F. H. K. Green, who was at that time the Council's Publications Officer; Dr. Green's other duties on the Council's administrative staff, particularly as Secretary of the War Wounds Committee (p. 28) and many of its sub-committees, stood him in good stead in assessing the accuracy and relative importance of the information contained in abstracts submitted for the Bulletin, and thus contributed materially to its reliability and practical value.

The *Bulletin of War Medicine*, started in September, 1940, at the request of the War Office, was essentially a successor to the monthly medical supplement to the official daily review of the foreign Press, which was compiled by the Medical Research Committee (the Council's predecessors) during the war of 1914-18, and continued by the Council, on a more comprehensive basis, as *Medical Science: Abstracts and Reviews* until September, 1925. It was, however, very much wider in its scope than the medical supplement, for in addition to abstracts of large numbers of publications from Allied and enemy countries, obtained through various channels during the war years, it included summaries of many hundreds of papers published in British periodicals, since by 1940 it had already become clear that medical officers in the field were often likely to be deprived of direct access even to such papers as the *British Medical Journal* and *The Lancet*. The Bulletin also served as the only means of publication, either *in extenso* or in abstract form, of many

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important official memoranda and reports prepared during the war years, which were not published separately.

The fact that the Bulletin was intended primarily for the assistance of Service medical officers cut off, by the circumstances of war, from direct access to original publications, made it very important that the information given in the abstracts should be full and accurate, and that details of such questions as the dosage of drugs should, when possible, be included. The need to ensure that such information was correctly given involved careful checking of the great majority of the contributions against the original sources, and it may fairly be claimed that the *Bulletin of War Medicine* attained through this precaution an exceptionally high standard of reliability; since the six volumes of the Bulletin comprised about 8,000 abstracts and some fifty original or review articles, it will be realised that the work of checking the accuracy of the contents was very onerous and time-consuming. It may be mentioned that similar precautions to ensure reliability are taken by the staff of the Bureau of Hygiene and Tropical Diseases in regard to the *Tropical Diseases Bulletin* and the *Bulletin of Hygiene,* the production of which is the Bureau's sole responsibility and continues to be its chief function.

It is of interest to record here that the *Bulletin of War Medicine* included throughout the war period a remarkable number of abstracts of papers published in German medical and surgical journals, of which often only single copies were available in Britain, thus assisting the medical authorities of the Allied countries to keep abreast with the enemy's published work in the field of war medicine. Of special importance is the fact that the Bulletin has provided a means of informing readers in the English-speaking countries of much of the work in the medical sciences done in the U.S.S.R. in recent years. The editors of the Bulletin were fortunate in finding abstractors who were not only experts in particular branches of medicine and surgery, but also had the requisite knowledge of Russian and other foreign languages. The Council are glad to know that the existing facilities for disseminating accurate accounts in English of the results of important work published originally in foreign journals have been augmented since the end of the war through the establishment by the British Medical Association of a new abstracting system, including two monthly publications, whose declared object is to maintain the traditions and functions of the Council's wartime Bulletin on an expanded basis under normal conditions.

Not the least valuable service performed by the *Bulletin of War Medicine* has been to supply workers who were deprived of a free international exchange of scientific information during the war years with a concise retrospective summary of a large proportion of the medical literature which they missed seeing in original; it is gratifying to report that many medical libraries and research institutions on the Continent of Europe have obtained complete sets of the Bulletin as a permanent work of reference from this point of view.

In sum, it may be stated that the six volumes of the *Bulletin of War Medicine* present a valuable critical survey of a very substantial part of the clinical and laboratory work in the medical sciences which was published or released for publication in Britain and many other countries during the period covered; and they should prove of particular assistance to those entrusted with the formidable task of writing medical histories of the war.

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XI

THE NATIONAL INSTITUTE FOR MEDICAL RESEARCH

Hampstead and Mill Hill, London

Staff in September, 1945

BIOCHEMISTRY

C. R. Harington, Ph.D., F.R.S. (*Director of the Institute*).
P. G. H. Gell, M.B.
R. K. Callow, D.Phil. (*on active service*).
A. Neuberger, M.D., Ph.D.
T. A. Webster.
Mrs. R. V. Pitt Rivers, Ph.D.
Miss J. M. L. Stephen, B.Sc.

CHEMOTHERAPY

(a) *Chemical*

H. King, D.Sc., F.R.S.
J. Walker, Ph.D., D.Phil.
T. S. Work, Ph.D.
Miss J. Crum, D.Phil.
H. S. Forrest, B.Sc.

(b) *Biological*

A. T. Fuller, Ph.D.
J. D. Fulton, M.B., Ph.D.
F. Hawking, D.M., D.T.M.
P. M. D'Arcy Hart, M.D., F.R.C.P. (*member of Council's external staff temporarily working at Institute*).
Mrs. J. Bedford, B.Sc.
Miss A. M. Burroughs, B.Sc.
Miss I. M. Tonkin, B.Sc.

PHYSIOLOGY AND PHARMACOLOGY

G. L. Brown, C.B.E., M.B., M.Sc., F.R.S.
F. C. MacIntosh, Ph.D.
W. D. M. Paton, B.M.

APPLIED PHYSIOLOGY

R. B. Bourdillon, C.B.E., M.C., A.F.C., D.M.
O. M. Lidwell, B.Sc., D.Phil.
J. E. Lovelock, B.Sc.

ENDOCRINOLOGY

A. S. Parkes, D.Sc., Sc.D., F.R.S.
C. W. Emmens, M.Sc., Ph.D. (*on active service*).
I. W. Rowlands, M.Sc., Ph.D.
Miss H. M. Bruce, B.Sc.

BACTERIOLOGY AND VIRUS RESEARCH

C. H. Andrewes, M.D., F.R.C.P., F.R.S.
F. Fulton, B.M.
R. E. Glover, M.A., F.R.C.V.S. (*Veterinary Officer*).
M. van den Ende, M.B., Ph.D.
P. Bruce White, B.Sc., F.R.S.
Miss R. Jackson, M.B.

PROTISTOLOGY

C. Dobell, Sc.D., F.R.S.

BIOPHYSICS AND PHYSICAL CHEMISTRY

A. S. McFarlane, M.B., B.Sc.
W. J. Elford, Ph.D.
J. Smiles, A.R.C.S.
D. Bunn, B.Sc., Ph.D.

BIOLOGICAL STANDARDS

Sir Percival Hartley, C.B.E., M.C., D.Sc., F.R.S.
D. G. Evans, M.Sc., Ph.D.

ADVISER ON INSTRUMENT CONSTRUCTION

E. J. H. Schuster, O.B.E., D.Sc. (*part-time*).

LIBRARY

Miss E. Wigmore, B.A., B.Sc.
Miss H. M. Clark.

ADMINISTRATION

D. K. M. Chalmers, M.D., D.P.H. (*on active service*).
A. R. Greaves.

Attached workers who were at the Institute between September, 1939, and August, 1945

BIOCHEMISTRY

Miss J. Allcock, B.Sc.

PHYSIOLOGY AND PHARMACOLOGY

F. Dickens, Ph.D., F.R.S. (*seconded by North of England Council of British Empire Cancer Campaign*).
C. B. B. Downman, B.Sc., M.R.C.S., L.R.C.P.
H. B. Barlow, B.A.

APPLIED PHYSIOLOGY

W. F. Raymond, B.Sc.

ENDOCRINOLOGY

A. Carlyle, B.V.Sc., M.R.C.V.S.
Mrs. A. S. Parkes, Ph.D. (Dr. R. Deanesly) (*part-time*).

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BACTERIOLOGY AND VIRUS RESEARCH

D. G. ff. Edward, M.D.
Mrs. J. van den Ende, B.Sc.
Miss D. M. Lush, B.Sc.
R. J. V. Pulvertaft, O.B.E., M.D., F.R.C.P.
Miss K. C. Mills.

BACTERIOLOGY AND VIRUS RESEARCH —*contd.*

A. M. Begg, M.B.
Mrs. F. Hamilton, B.Sc.

BIOLOGICAL STANDARDS

Lady Hartley, B.Sc. (*part-time*)

Visiting workers (*September,* 1939—*August,* 1945)

Mr. F. Alexander, M.R.C.V.S., Edinburgh.
Dr. E. C. Amoroso, Reading.
Dr. A. C. Crooke, London.
Miss J. G. Emmett, Nottingham.
Mr. M. E. Griffiths, M.Sc.
Mr. J. Hammond, Jnr., Cambridge.
Dr. N. P. Hudson, New York.
Dr. J. Le Beau, Paris.
Dr. I. Manton, Manchester.
Dr. C. J. O. Morris, London.
Dr. W. Nyka, Lwow.
Miss M. Outhwaite, Nottingham.
Dr. G. J. Schipper, Amsterdam.
Major C. H. Stuart-Harris, R.A.M.C.
Major - General Sir John Taylor, C.I.E., D.S.O., M.D., I.M.S. (retd.), London.

Miss B. R. Callow, M.A.
Dr. A. Felix, F.R.S. } Emergency Public Health Laboratory Service.

Surg. Lt. Cdr. F. P. Ellis, R.N.
Dr. W. Feldberg, F.R.S.
Surg. Lt. Cdr. Gay French, R.N.
Dr. J. A. B. Gray.
Surg. Lt. Cdr. P. G. Rowsell, R.N.
Dr. A. Sand, F.R.S.
Sq. Ldr. D. Williams, R.A.F.V.R. } Royal Naval Personnel Research.

Sub. A. Bargmann, A.T.S.
Major A. H. Hamilton Begg, R.A.M.C.
Major F. Buckland, R.A.M.C.
Dr. F. O. MacCallum.
Major Janet S. F. Niven, R.A.M.C. } Scrub Typhus Scheme—" Tyburn " Operation.

Summary of Research Work

In this section appears a summary of the research work carried out by members of the Council's staff and others, in the Institute at Hampstead and in the Farm Laboratories at Mill Hill during the period October, 1939, to September, 1945. Comparison with such summaries in earlier Reports will indicate the profound effect upon the activities of the staff which was exercised by the special conditions and demands of war. In certain of the Institute laboratories, notably that of physiology, the normal programme of research ceased completely at the outbreak of hostilities and the effort of members of the staff was directed almost entirely to the solution of special problems of immediate importance, many of them being of a short-term nature. In other divisions, such as that of virus research, the main work, while remaining fundamental in character, was re-orientated towards the study of diseases, such as the typhus fevers, which acquired special importance during the war; the virus research workers and others were also called upon to help in connection with practical problems of air hygiene. There is, indeed, no laboratory in the Institute of which the work was not in some degree affected, and members of the Council's staff working at the Institute were called upon to give a larger proportion of their time than usual to service on various committees. Nevertheless, it was possible to maintain certain lines of fundamental research during the war; and it is of some interest to note that even those researches which were directed towards the solution of immediate practical problems have not infrequently led to observations of intrinsic scientific interest which will repay further study under more normal conditions.

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A serious effect of the war upon the work of the Institute has been the further long delay imposed upon the completion of the new building at Mill Hill. Although the shell of this building was finished in 1942, its internal equipment for the purpose of scientific research could not at that time be contemplated. The building was therefore lent by the Council for use by the Admiralty as a training depot for the W.R.N.S. After three and a half years of occupation for this purpose, the building has now been vacated, and, at the time of writing, good progress has already been made with its preparation for final equipment. In the prevailing circumstances it is clear, however, that the process of completion will occupy a considerable time. During the period of delay, developments in the research work of the Institute have shown the necessity for larger provision than could have been foreseen for certain kinds of work, particularly of a physical character; this has been taken into account in an extensive re-planning of the laboratories in the new building.

Staff

On 1st October, 1942, there occurred the first change in the Directorship of the Institute, Sir Henry Dale retiring and being succeeded by Professor C. R. Harington. Fuller reference to this change is made elsewhere in this Report, as also to the very great loss which was suffered by the Institute by the death in 1940 of the Deputy Director, Sir Patrick Laidlaw.

On 31st March, 1944, Dr. J. Argyll Campbell retired from the service of the Council on reaching the age of 60. His activity during the last year of his appointment had been much restricted by ill-health, and he died a few weeks after his retirement. Dr. Campbell had been a member of the Council's staff since 1922; he will be chiefly remembered for a large volume of work on problems of anoxia (in particular, a study of the factors contributing to resistance of animals to low oxygen-pressures), and for his experiments on the rôle of dusts in the causation of cancer of the lung.

The Institute suffered a further loss in 1944, by the death, at the early age of 50, of Mr. H. P. Marks. Mr. Marks, who joined the staff in 1927, had done much valuable work on the assay of insulin, on which subject he was recognised as an authority.

Shortly before the outbreak of war, Miss M. Llewellyn Smith, who had given seven years of devoted and distinguished service to the Department of Biological Standards, left to be married. Besides assisting in the routine work, she had made a number of investigations on the antigens of *Staphylococcus*, of *Cl. perfringens* and of *Cl. tetani*, and on their corresponding antibodies. The results were of great practical importance, both at the time and in the later development of the work on gas gangrene, tetanus, and the stability of antitoxins, carried out in the Department.

A short while after her marriage Miss W. I. Strangeways (now Mrs. Surgey), after eleven years' service, left the Council's employment early in 1940. Miss Strangeways took part in the programme on the chemotherapy of trypanosomiasis, and she was also responsible for studies bearing on the biological control of the arsphenamines.

In December, 1942, Dr. F. G. Young left the Institute to take up the appointment of Professor of Biochemistry at St. Thomas's Hospital Medical School. Dr. Young had worked at Hampstead since 1936, and during his period of service as a member of the staff he had established his reputation as a leading worker in endocrinology, by his study of the hormones of the anterior pituitary gland. Particular mention may be made of his experimental production of permanent diabetes in dogs.

Dr. C. Rimington, who was appointed to the staff in 1937, left in April, 1944, to become Professor of Chemical Pathology at University College Hospital

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Medical School. While at the Institute, Dr. Rimington developed the work on animal pigments for which he was already well known, and he made other important contributions to biochemical knowledge, particularly on serum gonadotrophin.

Dr. I. W. Rowlands left the Institute in 1945 to join the staff of the Wellcome Foundation. Dr. Rowlands entered the laboratory of endocrinology as an attached worker in 1933, and was appointed to the staff in 1937. His work was concerned mainly with the biological assay of hormones, particularly the gonadotrophins, and later with factors affecting fertilisation.

Dr. M. van den Ende, who was appointed to the established staff in 1939, has left to return to South Africa, as Professor of Bacteriology in the University of Capetown. After working on immunological problems, Dr. van den Ende transferred his activities, on the outbreak of war, to research in air-disinfection. Later he joined the team of workers on typhus fever, taking part in an expedition to North Africa and Italy for the study of the chemotherapy of this disease. During the last year of his appointment, he was seconded to the Wellcome Foundation, on whose behalf he took charge of the large-scale production of scrub typhus vaccine (p. 213).

In addition to the present Director, the following have been appointed to the Council's established scientific staff for work at the National Institute, during the period covered by this Report: Dr. J. Walker, Dr. T. S. Work and Dr. F. Hawking (Chemotherapy); Dr. F. C. MacIntosh (Physiology and Pharmacology); Dr. C. W. Emmens (Endocrinology); Dr. D. G. Evans (Biological Standards); Dr. A. Neuberger and Dr. P. G. H. Gell (Biochemistry); Dr. A. S. McFarlane (Biophysics and Physical Chemistry); and Dr. F. Fulton (Bacteriology and Virus Research).

Since the end of the period under review, Sir Percival Hartley has retired from the post of Director of Biological Standards, being succeeded by Dr. A. A. Miles.

In the first Annual Report of the Medical Research Committee (the predecessors of the Council) it was noted that the formation of a Library was already being considered. In the Report for 1917-18, despite the difficulties of the times, the Committee were able to record that the nucleus of a Library had already been formed. By 1919-20 the Library was housed in a room temporarily fitted for the purpose, and a year later there were between three and four thousand bound volumes in the Library, which was permanently equipped. Since 1920 the Library has continued to grow apace. It has been replanned, redecorated and extended more than once, and is now one of the largest and best-ordered medical and scientific libraries in the country. Results such as these are not attained without effort, and the person mainly responsible for the successful establishment of the present Library was its first Librarian, Miss K. Baverstock. She came to Hampstead from the Council's Statistical Department, bringing with her the original books belonging to that Department, and before the Institute was in working order she was already busy collecting, arranging, cataloguing and planning for future needs. With the support of the Library Committee, she continued to organise and expand the Library until her retirement in 1942. The Council, and all senior members of the scientific staff, are well aware of the part which Miss Baverstock played in the foundation and development of the Library as an efficient instrument of research. They also appreciate how much of the present friendly and fruitful relations of the Institute Library with other libraries, and with research workers within and without the Institute, is directly due to her hard work, knowledge and tact. Miss Baverstock's long and devoted labours and services are therefore now recorded and acknowledged with gratitude.

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On Miss Baverstock's retirement, the post of Librarian was filled by the appointment of Miss Ethel Wigmore, and in July, 1945, the Library staff was further strengthened by the appointment of Miss Hilda Clark, a former member of the library staff at the London School of Hygiene and Tropical Medicine, as Assistant Librarian at the Institute.

In concluding this survey of the staff changes at the Institute during the war, the Council wish to record their regret at the deaths of Miss Dora Lush of Melbourne, and Dr. A. Sand who, though not members of the staff, had taken part in the Institute's research programme as visiting workers. Miss Lush, whose valuable co-operation in the studies of influenza and of problems of air hygiene is noticed on pp. 210 and 213, died from a laboratory infection with scrub typhus shortly after her return to Australia. Dr. Sand, at the time of his death, was collaborating with Dr. G. L. Brown and his colleagues in some of the work for the Royal Naval Personnel Research Committee which is outlined below.

Personnel Researches

The outbreak of war led immediately to suspension of the normal activities of the physiological laboratory, which had been mainly directed to the study of neuro-muscular physiology. In the early months of the war Sir Henry Dale and his colleagues were concerned with problems connected with traumatic shock, such as the use of haemoglobin solution as a blood substitute.

With the increasing realisation, early in 1940, of the importance of physiological factors for the efficiency of the fighting man in modern warfare there came the formation of the Military Personnel Research Committee (p. 134), and from that time until late in 1942 Dr. Brown and Dr. MacIntosh were occupied with problems of immediate military importance. The design and testing of body armour and steel helmets was undertaken, much of the work on the latter subject being done at the Institute. During periods of secondment to the laboratory at Lulworth, Dr. Brown took part in the work on the development of the all-round vision tank cupola, and Dr. MacIntosh studied carbon monoxide poisoning as a hazard to tank crews.

The most profound effect on the work of the laboratory was exercised, however, by the formation in December, 1942, of the Royal Naval Personnel Research Committee, of which Dr. Brown became Secretary. From the time when this Committee was appointed until late in 1945, almost the entire effort of Dr. Brown and his colleagues, together with numerous attached workers, was directed towards the solution of physiological problems affecting naval operations. The main theme of the work has been under-water physiology, *i.e.*, the physiology of submarine crews and more particularly of special service divers using self-contained diving gear. The urgency of the latter problem lay in the need to define, and if practicable to increase, the possible range and depth of operation of the one-man submarine which was at that time under development.

The problem resolved itself into a study of the physiological effects of high oxygen tension, and it was attacked at the Institute in a variety of ways. The large pressure chamber used formerly by Haldane, Damant and Boycott, in their classical work on compressed air sickness, was transferred to the Institute and has been operated extensively throughout the research, more than 300 " dives " having been taken. This pressure tank was used for the study of the effects of oxygen poisoning on human beings, and for the attempt to obtain a closer analysis of these effects by experiments on small animals and by the investigation of the respiration of tissue slices.

At the outset of the work, one of the chief difficulties recognised was the extreme variability in the resistance of human subjects to the effects of oxygen poisoning, and it was hoped by experimental methods to discover

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both the reasons for this variability and methods for controlling it. The results of the work on human subjects, in which Dr. C. B. B. Downman took part, were on the whole disappointing. Although reasonably constant changes in the cardiovascular system and in neurological signs occur during oxygen intoxication, these are not individually of sufficient magnitude to make it possible to predict whether the end-point of a subject's tolerance to oxygen will be an unheralded convulsion, or whether the convulsion will be preceded at an indefinite interval by the twitching of peripheral muscles which in some subjects serves as a sign of warning.

Electro-encephalographic observations by Squadron Leader Denis Williams showed that the terminal convulsions in oxygen poisoning were identical with those occurring in grand mal epilepsy; the prodromal twitching referred to above was without a cortical accompaniment. In spite of the epileptiform nature of the convulsions, however, epileptic subjects having grossly abnormal encephalograms showed tolerance to oxygen well within the normal limits. Electro-encephalography therefore did not offer an objective means of selecting oxygen-resistant personnel.

In view of the nature of the symptoms of oxygen poisoning, it was thought that anti-convulsants might be useful in delaying their onset. This was indeed found to be the case by Mr. Marks, who showed that bromides and certain barbiturates which are effective in epilepsy significantly increased the tolerance of mice (which are, in any case, much more resistant than human subjects); curiously enough, diphenylhydantoin, which is used in the treatment of epilepsy, was without effect in oxygen poisoning. Here again, however, the results could not be extended to man; although the experiments were not prolonged intentionally to the convulsive stage, the onset of prodromal symptoms in subjects habitually showing these was not delayed by treatment with bromide or phenobarbitone.

In extensive experiments on the respiration of slices of brain tissue, Dr. Dickens was able to demonstrate the poisoning effect of oxygen, and to show that this was due at least in part to the inhibition of certain enzymes concerned in carbohydrate metabolism, particularly succinic dehydrogenase, triosephosphate dehydrogenase, pyruvate oxidase and phosphoglucomutase. He also showed that the enzymes could be protected by cobalt and manganese ions. The protective effect of cobalt could be demonstrated in mice, but these were protected also by zinc, which had the reverse effect on tissue slices; the mechanism of these ionic effects therefore remained obscure, and no question could arise of their practical application in the human subject.

When it became clear, as the result of these experiments, that no simple solution of the problem of oxygen poisoning would be quickly forthcoming, the work which had been done at the Institute, together with that of the Admiralty Experimental Diving Unit, was used for the important practical purpose of defining the safe limits of time and depth of operation of divers using pure oxygen.

A further practical problem studied at the Institute was the reason for the loss of consciousness which occurred in divers supplied with oxygen when they were at quite shallow depths but were doing hard work. The symptoms shown by these men were quite different from those of oxygen poisoning, nor could they be ascribed to lack of oxygen; an experimental study by Dr. MacIntosh and Mr. Barlow showed that accumulation of carbon dioxide was the probable cause. This led to new observations on the subject of carbon dioxide intoxication, which not only entirely confirmed the supposition that carbon dioxide was the responsible agent but proved to be of considerable scientific interest. The effect of carbon dioxide which has received most attention from physiologists is the stimulation of respiration

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which occurs when it is breathed with air containing less than the normal amount of oxygen; preoccupation with this respiratory effect led to neglect of the cerebral effects of high concentrations of the gas, which were described by Paul Bert in 1887. It is evident from the work of Dr. MacIntosh and Mr. Barlow that, when breathed together with oxygen in concentrations as high as or higher than that present in ordinary air, carbon dioxide is a general anaesthetic and can cause loss of consciousness unheralded by respiratory distress.

Further confirmation of the responsibility of carbon dioxide for the loss of consciousness of divers at shallow depths was provided by the estimations by Dr. Paton and Dr. Sand of the metabolism of men working a static ergometer under water; it was found that under these conditions the output of carbon dioxide was some three times as great as had been supposed; moreover, quantitative assessment of the performance of existing self-contained diving gear in removing expired carbon dioxide revealed a considerable lack of efficiency. The practical outcome of this work was the design by Dr. MacIntosh, in consultation with the Chemical Defence Research Experimental Station, of an improved apparatus for carbon dioxide absorption, which has since proved satisfactory under operational conditions.

Ancillary to the investigation just described was a study by Dr. Paton and Dr. Sand of the conditions of respiration in the immersed subject; as the result of this, they were able to define the optimum intrapulmonary pressure for the diver, and incidentally to obtain useful information on muscular work and efficiency under water.

In addition to the major problems outlined above, a number of purely practical questions have been studied in the laboratory. Thus Surgeon Lieut.-Commander Gay French was able, as the result of work which he did in the Institute on the causes of otitic barotrauma in divers, to lay down provisions for training and instruction which have diminished the incidence of this ear trouble. Dr. MacIntosh has investigated the conditions in submarines when submerged, and has also studied the tolerance of divers to temperatures likely to be met with in tropical seas. Dr. Gray has tested the effects of carbon dioxide on men working under the conditions which obtain in naval gun turrets.

The whole of the work which has been described has been done under the general direction of Dr. Brown. It owes much not only to the investigators whose names have been mentioned, but also to the assistants who have worked with enthusiasm and competence and with a fine disregard of personal discomfort throughout.

Although the entire orientation of the personnel research has been towards practical objectives of immediate importance, it has already been pointed out that some of the results obtained are also of great intrinsic scientific interest. Thus the observations of Dr. Dickens on the effects of oxygen poisoning on enzyme systems of the brain raise points which invite further study, and the anaesthetic effect of carbon dioxide might well have remained unrevealed but for the work on shallow diving. These are notable examples of the way in which properly directed applied research may lead to advances in fundamental science.

Another aspect of personnel research which may be mentioned at this point was initiated by a request from the Military Personnel Research Committee for tests of certain pastes which had been suggested as possibly suitable for protecting the faces and hands of troops exposed to attack by flame-throwers. This led to the very extensive investigations by Dr. Bourdillon and his colleagues of the whole problem of protection against flame, which have been briefly noticed on pp. 45 and 136. Quantitative methods were

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developed for assessing the effects of flame, and protective measures were devised for the various operational conditions which were envisaged. These measures were studied by Dr. Bourdillon in field trials arranged by the Service Departments concerned.

As the result of this work it was possible for Dr. Bourdillon not only to advise on the most suitable types of protective clothing for troops exposed to flame attacks, but also to give reasonably close estimates of the maximum time of tolerance to such exposure which might be expected. Although the work did not have the fundamental scientific interest of that which was carried out for the naval personnel research, it was clearly of great potential importance for the reduction of casualties. Moreover, its execution demanded a high degree of personal courage and of technical ingenuity.

Whilst it will be clear from what has been said that the activities of the physiological laboratory during the war years have been almost entirely concerned with special problems, the ordinary work of the laboratory in connection with Biological Standards (p. 242) was not allowed to lapse. Moreover, up to the time of his retirement, Dr. Argyll Campbell continued his studies of the mechanism of production of resistance to anoxia in rats; he was not able to reach a final conclusion as to the nature of the beneficial effect of a carrot diet in this respect to which reference has been made in previous Reports.

Influenza

Work on influenza continued at Hampstead throughout the war. Garglings and serum samples from patients with influenza were examined in order to determine the nature of the infection prevalent each year. In 1940 American workers discovered a new virus strain, serologically unrelated to that first isolated here in 1933: the original strain was named " A " and the new one " B ". Examination of sera held at Hampstead in the cold box showed that some of the influenza in this country in the spring of 1939 must have been caused by the " new " B virus. In the winter of 1939-40 studies were difficult owing to dispersal of staff; one virus A strain was recovered from material sent from Flanders. In 1940-41 there was a minor winter outbreak in which virus A was concerned. No influenza appeared in the following winter; but in that of 1942-43 another minor epidemic occurred. Virus B seemed to be the agent chiefly responsible, but at the end of the spring, and through the summer, occasional local A outbreaks were recognised. These led up to the only considerable wartime epidemic of influenza in Britain, the A epidemic of October to December, 1943: even this was not very severe, and no further epidemic occurred during the war. The influenza periodicity apparently established before the war was upset, with the fortunate result that epidemics were rather less frequent during the war than before it.

In 1940 a complex vaccine was reported from the U.S.A. to have promise against influenza, and, through the generosity of the Rockefeller Foundation, several hundred thousand doses were provided for trial in this country; 193,900 doses were distributed to the Services for test in 1940-41, but no influenza occurred in the vaccinated groups, to enable a decision to be reached as to the value of the vaccine. Later work in America threw doubt on the value of this particular vaccine, but another type, developed later, gave much better results there. This is now on trial in Britain.

Those continuously concerned in the work above described on the identification of viruses in epidemics, and in vaccine trials, were Dr. C. H. Andrewes and Mr. R. E. Glover. They were assisted by several visiting workers: Miss Dora Lush of Melbourne, Australia, from 1940 to 1942; Dr. N. P. Hudson of the Rockefeller Foundation from 1940 to 1942; Miss K. C. Mills from Columbia University, New York, from 1942 to 1943; Mrs. F. Hamilton from McGill

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University, Montreal, from 1943 to 1945; Major (later Colonel) C. H. Stuart-Harris, working in Army laboratories, collaborated closely with workers at Hampstead.

Other investigations on influenza, of a more academic nature, can be mentioned only briefly: Dr. Andrewes, Dr. King and Dr. van den Ende tested 115 compounds for chemotherapeutic activity against the virus—all with negative results; Mr. Glover and Dr. Andrewes found that swine influenza virus from this country was as closely related to human strains as to American strains of swine influenza; Dr. Andrewes found that an influenza virus growing in tissue cultures could interfere with or suppress the growth of another biological race of the virus subsequently added to the culture; other studies are mentioned in the section on air-borne infection.

Typhus Fever

Work carried out during the war included search for chemotherapeutic agents active against typhus, antigenic studies in relation to vaccination, and the development of an immunising vaccine against scrub typhus. Close contact was maintained with Army workers, especially those at the Royal Army Medical College Emergency Vaccine Laboratory at Everleigh. Information was freely exchanged with workers in the same field in Canada and the U.S.A. In promoting research on typhus, from 1943 till the end of the war, the Council were advised by a special Committee (p. 416) under the Chairmanship of Major-General L. T. Poole.

Methods of study.—The undertaking of work on typhus at the National Institute necessitated the adoption of elaborate precautions against the spread of infection from inoculated animals. At first, work in the Institute was confined to the murine virus and the more dangerous epidemic virus was studied only in special accommodation at the Farm laboratories at Mill Hill. Later, when workers had become familiar with methods of handling the infection, all the work was transferred to Hampstead. There the typhus laboratories formed a self-contained unit; the infected animals were also housed in a separate unit in the animal house, the cubicles of which opened only to an outside balcony. Workers wore special gowns and, for more dangerous manipulations, masks and gloves. Special methods were devised for safely disposing of all infected material. Despite these precautions, and despite inoculation with the best typhus vaccines then available, five workers became infected with murine typhus soon after work was begun in 1942. The source of these infections almost certainly consisted of air-borne rickettsiae exhaled by mice which had just been inoculated intranasally. Subsequently, Dr. van den Ende—with the help of Dr. Bourdillon and Mr. Hubbard—devised an inoculation box so constructed as to ensure that all air leaving the chamber was first sterilised by heat. Boxes of this type were used in all later work, and during the next four years only two further clinical infections occurred.

The work carried out included the cultivation of rickettsiae in the yolk-sacs of developing hens' eggs, infection of guinea-pigs and intranasal infection of mice and other animals. For the latter purpose, Dr. van den Ende adapted a technique first used by Burnet and Rudd in studies of psittacosis. It was found that mice inoculated intranasally with dilute rickettsial suspensions developed in their lungs discrete grey spots, whose numbers were sufficiently reproducible for accurate quantitative work (spot count technique). The numbers of spots were reduced in the presence of immune serum, and a " neutralisation-test " for the detection of antibody was devised by Dr. van den Ende and Miss Mills; this gave results of much interest in comparison with other methods of assaying typhus antibodies.

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Chemotherapy.—The spot count method was used as the basis of chemotherapeutic studies on typhus by Dr. Andrewes, Dr. King and Dr. van den Ende. Mice were infected intranasally with typhus, and injected with test drugs over a period of several days; reduction seen in the spot count when they were killed a week later was used as an index of the efficacy of the compound. Seventy compounds of various types, from commercial and other sources, were tested without the detection of any activity. Then, in November, 1942, two compounds—*p*-sulphonamidobenzamidine (V147) and the corresponding amidoxime (V186)—were found to have very considerable potency; further reference to the extensive programme of chemotherapeutic study resulting from this finding is made on p. 215. The toxicity of the active drugs for animals and man was examined, and it was felt that the results were sufficiently encouraging to call for a field trial in human cases of typhus fever. A joint Army-Medical Research Council team, consisting of Major C. H. Stuart-Harris and Major van den Ende, R.A.M.C., later joined by Major M. H. Gleeson White, R.A.M.C., and Captain W. L. Hawley, M.C.A.U.S., went to Algiers for this purpose; their activities were transferred to Naples when typhus broke out there in December, 1943. The drugs, particularly V 186, were given to civilian cases in hospital; of alternate patients admitted with typhus, one received the drug, the next being given orthodox supporting treatment only. Unfortunately, no benefit from the drug treatment was noted, one adverse factor being the difficulty in obtaining cases for treatment within the first few days of the onset of the disease. The detailed clinical, haematological and biochemical studies of typhus made during these trials form a valuable record and, together with data on serological and histological material subsequently examined, have been published in the Council's *Special Report Series* No. 255; the report also includes accounts of various important studies in the immunology of typhus made by members of the Council's staff. The chemotherapy of infections due to viruses and other intracellular parasites is a matter arousing much interest at present: though the practical results from the work on V 147 and V 186 turned out to be disappointing, the finding of highly specific activity in these two substances is of great scientific interest and may ultimately lead to important advances in a very difficult field.

Immunological studies.—Manufacture of typhus vaccines in eggs was being carried out overseas—especially in Canada and the U.S.A., where eggs were more plentiful than in Great Britain. Studies bearing on active immunisation against typhus were, however, made also at Hampstead.

The war provided an opportunity of bringing together, for comparison, typhus strains from many parts of the world. Immunological tests carried out by several methods showed that epidemic typhus strains were antigenically indistinguishable, whether coming from Poland, Russia, Iran, Irak, Egypt, North Africa, Italy, Syria or Palestine; this fact, which was not known for certain before, indicates that one type of vaccine should protect against the disease anywhere in the world.

Careful antigenic studies by Dr. Forrest Fulton and Dr. Begg elucidated the relationships between the murine and epidemic types of rickettsiae, and between these and *Proteus OX 19*, the bacillary strain used in the Weil-Felix test. Surface antigens of either strain of rickettsiae seemed to give rise to a heterogeneous group of antibodies, some of which were strain-specific while others reacted with the other strain. Boiled suspensions acquired a new specificity, that was the same whichever strain was employed. The *OX 19* antibody was shown to be related to the antibodies reacting with the boiled antigen, not to those of the intact surface of the organisms.

Other laboratory studies of typhus at the Institute can be mentioned only briefly here. Dr. Fulton, Dr. van den Ende and Dr. Elford, with Miss Mills.

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investigated different methods of estimating the potency of typhus vaccines in the laboratory. Dr. Begg, Dr. Fulton and Dr. van den Ende studied the inclusion bodies formed in the lungs of typhus-infected rodents. Dr. Elford and Dr. van den Ende determined the filterability of typhus rickettsiae. Lieut. Nyka, of the Polish Army, worked for six months at the Institute, studying methods of demonstrating rickettsiae in tissues.

Scrub Typhus

Though epidemic typhus proved much less of a menace to our military forces than had been feared, a related disease, scrub typhus, or tsutsugamushi disease, caused unexpected and very serious trouble especially in New Guinea and Burma, and even in areas such as Ceylon and the Maldive Islands, where its existence was previously unsuspected. Attempts had failed to find a vaccine on lines which had proved successful for epidemic typhus: accordingly, fresh efforts were made by workers at Hampstead. Dr. Forrest Fulton and Mr. Joyner ultimately succeeded in making a vaccine of high rickettsial content from the lungs of cotton rats, and this was effective in protecting mice against scrub typhus in the laboratory. Precautions previously worked out in the studies of epidemic typhus, and supplemented by the use of bactericidal aerosols (see below), enabled the team to work safely with this still more dangerous disease.

Reference has already been made (p. 66) to the decision, on military grounds, to undertake large-scale production of the cotton rat vaccine even in the absence of evidence of its efficacy in the human disease. In the organisation of this formidable project, undertaken by the Wellcome Foundation on behalf of the Ministry of Supply, the staff of the Institute played a prominent part. Not only was Dr. van den Ende seconded to take charge of the operation (which was given the secret code name of " Tyburn "), but Dr. Rowlands was made responsible for the animal colony and Dr. Bourdillon gave essential advice on the vitally important question of air disinfection on which depended the safety of the workers. The large numbers of A.T.S. personnel who were required for the production work were given a preliminary period of training in the laboratories of the Institute.

Air-borne Infection

Early in the war the late Sir Patrick Laidlaw initiated a comprehensive series of studies on methods of preventing air-borne infection; the risk of such infection seemed likely to be especially great where large numbers of persons were confined under crowded conditions as in air-raid shelters; the need for defence against the potential threat of bacteriological warfare also had to be considered.

At the beginning, the behaviour of very fine mists containing bacteria or viruses was studied in comparatively small containers, and quantitative techniques were evolved (Dr. Edward, Dr. Elford and Sir P. Laidlaw). Methods of killing the organisms with ultra-violet radiation (Dr. Edward, Miss Lush and Dr. Bourdillon) or with chemical aerosols (Dr. Edward and Dr. Lidwell) were studied. Dr. Elford, with Dr. Todd and later Mrs. van den Ende, then took the investigation further by studying larger volumes of mists in air-tight tanks: Dr. Pulvertaft and later Dr. Elford proceeded to make similar observations in specially designed spray rooms. These studies particularly concerned the conditions, such as those of temperature and humidity, under which organisms could survive as particles suspended in the air, and under which various chemical aerosols and ultra-violet radiation could destroy them. The merits of ozone as an aerial disinfectant were studied by Dr. Elford and Mrs. van den Ende, and it was concluded that this gas was really effective only in concentrations which were not tolerable to human beings.

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Mr. Glover and Dr. Andrewes studied the emission of infective particles (influenza virus and streptococci) from the respiratory tracts of infected ferrets both in small cubicles and in ducts of various forms. Evidence was obtained of transmission of infection by means of very fine particles (droplet nuclei), and experiments were carried out on stopping cross-infections by means of screens, ultra-violet radiation and chemical aerosols.

An important fact emerging from the early work, and not well emphasised in the literature, was the resistance of dry dust-borne organisms to physical and chemical disinfectants. Because of this resistance, treatment of the air by means which had seemed excellent in the laboratory failed to achieve its objects in trials under practical conditions. Dr. van den Ende, with Dr. Edward and Miss Lush, made a series of experiments on the control of dust, which formed the basis of perhaps the most immediately useful measures to arise out of all these earlier investigations. Major J. C. Thomas, R.A.M.C., later collaborated with them in field trials.

Blankets and other textiles were impregnated with streptococcal cultures, and a technique was devised for studying quantitatively the dispersal of the organisms into the air when the textiles were beaten, and the subsequent re-dispersal of the infected dust which had settled on the floor. As a result, methods were developed for dealing with the dust problem by treating blankets and floors with oils; after such treatment, dust was not readily dispersed when blankets were shaken, and the dust on floors was aggregated into balls which could be swept away without liberation of clouds of bacteria-laden particles into the air. Oiling of floors, and to a lesser extent of blankets, has since been used in hospitals as a method of preventing cross-infection, and the work is now being extensively developed in the U.S.A. Substantial reduction has been obtained in the numbers of organisms in the air of hospital wards, particularly in the numbers dispersed by bed-making and there is some evidence that cross-infection of patients has been reduced.

At the time when the researches on typhus fever were begun, the direction of the work on air-borne infection passed to Dr. Bourdillon, who had already been collaborating in it for about a year. Dr. Bourdillon was helped in these studies by Dr. Lidwell, Mr. Lovelock and later Mr. Raymond. In the early stages of the investigation Dr. Bourdillon attacked the problem of the quantitative estimation of air-borne bacteria; for this purpose he devised an apparatus —the "slit-sampler"—which has been used throughout the work. This instrument has proved to be exceptionally convenient for taking large numbers of samples, and it allows of much better timing of changes in bacterial concentration than any other system yet devised. The general recognition of the practial value of the slit-sampler is shown by the large numbers which have had to be constructed in the Institute for use by outside workers, and by the fact that the instrument is now being manufactured commercially.

Considerable attention was given to the design of a series of sprays which could be used for the disinfection of closed spaces such as air-raid shelters with hypochlorous acid. An extremely simple method for the evolution of this bactericidal agent was devised, which could have been used all over the country if necessary at short notice: it consisted of boiling bleaching powder with dilute alkaline phosphate solution, and for small spaces it required no more apparatus than a tin and a spirit lamp.

A discovery which promises to be of major importance for chemical air disinfection is the observation by Mr. Lovelock of the powerful effect of aliphatic hydroxy-acids (lactic acid and its homologues). Although, in common with other air disinfectants, lactic acid is less effective in very dry air, at the relative humidities usually prevalent in this country, and at tolerable concentrations, it kills air-borne bacteria at an exceedingly high rate, reducing their

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concentration to less than 1/2000 of the initial value in six minutes. Moreover, lactic acid has the great advantage of being entirely non-toxic to the human being in the concentration needed for bactericidal effect.

Extensive studies of other methods of air disinfection led to the conclusion that, apart from such chemical disinfectants as lactic acid, ultra-violet light offers the greatest possibilities for inhabited spaces. For disinfection of air carrying dangerous organisms in certain industrial and laboratory operations, heat sterilisation can be applied; the experimental work of Dr. Bourdillon and his colleagues on this question has shown that complete sterilisation is obtained by raising the temperature of air to 225°C.; by the use of a regenerative furnace, large volumes of air can be dealt with in this manner, and the method was in fact employed in connection with the large-scale production of scrub typhus vaccine.

The problem of freeing air from bacteria can also be attacked by preventive methods. Investigations carried out by Dr. Bourdillon in various hospital operating theatres, and particularly in collaboration with Dr. Colebrook in the Council's Burns Unit at Birmingham (p. 271), have shown that the risk of air-borne infections can be greatly reduced by the installation of a plenum ventilating system combined with efficient air filtration. The application of similar methods in two penicillin production plants did much to obviate failures due to contamination with air-borne organisms. As a result of the work which has been described, together with surveys of the conditions in factories, offices, hospital wards and other places, the position has been reached in which it is possible to replace the present empirical standards of ventilation with an objective definition based on the maximum tolerable number of air-borne organisms.

It is generally recognised that in a crowded community much respiratory disease is spread by direct droplet infection, but objective data have hitherto been lacking. Such data have now been provided by quantitative studies of the effects of sneezing. These showed that a single sneeze might project 100,000 infected droplets, of which, in a closed room, as many as 4,000 might still be floating half-an-hour afterwards. Flash photographs of sneezes, demonstrating their liability to spread infection, were taken at the Institute and were extensively used for propaganda purposes by the Ministry of Health. In connection with this work a simple form of transparent plastic mask was designed for use by persons in air-raid shelters in the event of an epidemic of respiratory disease.

The results of several of the investigations noticed above have already been published in the medical press. An account of many other aspects of the recent studies in air hygiene by members of the Council's staff and their co-workers is being published as a monograph in the Council's *Special Report Series*.

Chemotherapy

Virus and rickettsial diseases.—An attack on the chemotherapy of virus diseases was begun in 1940. During the first two years' work, a very large number of compounds selected by Dr. King was tested by Dr. Andrewes and Dr. van den Ende against experimental infections with influenza in mice and with vaccinia and lymphogranuloma venereum in rabbits; the only positive result obtained was a confirmation of the known effect of sulphonamides in experimental lymphogranuloma infection. When work on typhus was started in the Institute, an intensive search for anti-rickettsial chemotherapeutic agents was begun, and this led in 1942 to the discovery that *p*-sulphonamidobenzamidine (designated V147), a compound which had been prepared by the late Dr. F. L. Pyman of Boots Pure Drug Co., Ltd.,

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and was known to be an active anti-streptococcal agent, was effective against experimental typhus infections in mice (see p. 212 above). An attempt was immediately made by Dr. King and Dr. Walker to exploit this observation; in the course of a long programme of synthetic work it was found that, unlike the anti-bacterial activity of the familiar sulphonamides, the anti-rickettsial activity in this series was highly specific, being completely abolished, for instance, by substitution of the hydrogen atoms of the sulphonamide group to form analogues of sulphapyridine and sulphathiazole. Activity was also largely or completely destroyed by interposition of a methylene group between the benzene ring and the sulphonamide or amidine groups. The only compound found to have activity equal to that of the original sulphonamidobenzamidine was the corresponding amidoxime (V186), and this was subjected to clinical trial as described elsewhere in this Report.

Dr. King and Dr. Andrewes have collaborated in a study of the anti-rickettsial action of dyes of the methylene blue type, without, however, finding any favourable lead for chemotherapeutic development.

Despite the great difficulties of chemotherapy in virus diseases, and despite the failure of V147 and V186 to cure human typhus, the finding that these compounds are active in the experimental infection is very encouraging: it seems to dispose of the theoretical argument that chemotherapeutic attack is foredoomed to failure in the case of an obligatory intracellular parasite depending upon the metabolism of the host cell.

Anaerobic and other wound infections.—In the course of the chemical studies arising from the observation of the anti-rickettsial activity of *p*-sulphonamidobenzamidine, Dr. Walker prepared a series of compounds in which the sulphonamido group was replaced by the methylsulphonyl group. One of these, *p*-methylsulphonylbenzamidine (V187) was found by Dr. Fuller to have high antibacterial activity, particularly against anaerobic organisms. This led to a collaborative study with Dr. Evans, as the result of which it was found that this compound was an effective chemotherapeutic agent against experimental infections of the guineapig with *Cl. welchii, Cl. oedematiens* and *Cl. septicum;* later, V187 was also shown to be active against experimental tetanus infections. It has not yet been ascertained whether this drug is of value in clostridial infections in man, since the clinical trials which were projected for the European campaign were forestalled by the advent of penicillin. Laboratory tests have further shown V187 to be active against sulphonamide-resistant streptococci, and it is hoped that information on its clinical uses in infections by these and other bacteria will be forthcoming from work to be carried out in India. In the meantime, Dr. Walker has made a detailed study of the structural requirements for anti-bacterial activity in the sulphone group of compounds.

An extensive programme of experimental work on the use of the better known sulphonamide drugs to prevent or treat wound infections was carried out by Dr. Hawking during the first four years of the war. The studies included observations of the histological effects of various preparations of sulphonamides and other antiseptics; the rates of absorption and excretion of sulphonamides of different kinds, and in different forms, were examined in collaboration with Dr. Fuller. In experimental wounds in guinea-pigs infected with the organisms of gas gangrene, Dr. Hawking found that the insertion of powdered sulphonamides into the wound at the time of infection protected most of the animals against massive infections with *Cl. welchii* or *Cl. septicum,* but was of little value against infections by *Cl. oedematiens;*

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if the treatment were delayed until a few hours after infection, its value was much diminished; local application was more effective than systemic administration; sulphathiazole was more effective than sulphapyridine, which, in turn, was better than sulphanilamide. In view of this, and of the shortage of sulphathiazole at that time (1941-42), it was recommended that wounds should be treated locally with a mixture of sulphathiazole and sulphanilamide. Similar work was later done on experimental wounds in rabbits infected with streptococci; in these also, sulphathiazole proved to be the most effective sulphonamide for preventing local and systemic infections. This work led to a study of what happened to a sulphonamide when it was placed in a wound. It was shown that the drug spread fairly easily through the main cavity of the wound, but penetrated only with difficulty into the crevices or into dead tissue; living tissue with an active circulation was not affected by the drug except on the surface. Further studies were stimulated by a suggestion of Lieut.-Col. A. J. Gardham, R.A.M.C., that when battle conditions made early surgical treatment impossible, the wounds might usefully be filled with some semi-liquid sulphonamide preparation as an interim prophylactic measure against infection. After a long study of many types of sulphonamide pastes from various points of view, the microcrystalline suspension of sulphathiazole was recommended as the most effective preparation therapeutically, and as the least likely to have adverse effects on the tissues; all the oils and oily preparations tested were found to cause undesirable tissue reactions, cotton seed oil being the least injurious of those tried.

Although microcrystalline sulphathiazole was used with success for certain surgical purposes, practical difficulties prevented its extensive field trial in the wounded, and the need to consider its use for the prophylaxis of wound infection was obviated when penicillin became widely available.

Malaria.—Dr. King and Dr. Work have extended the earlier investigations of Dr. Ainley and Dr. King on the synthesis of compounds of quinine type; it has been found that antimalarial activity, as shown by tests on bird malaria by Dr. Ann Bishop at the Molteno Institute, Cambridge (p. 311), is present in carbinolamines more accessible to synthesis than the compounds made by Ainley and King. During the war a sample of the new German antimalarial " Sontochin " was secured, and Dr. King and Dr. Work were able to establish its identity. Dr. Work has also devoted much attention to the synthesis of compounds resembling niquidine, a base derived from quinidine, and has successfully synthesised an isomeric dihydroniquidine with antimalarial activity comparable with that of quinine. Unfortunately the smallness of the yield obtained has precluded its clinical trial in malaria. Through the co-operation of the British Council, a quantity of the Chinese drug, Changshan, derived from *Dichroa febrifuga,* was secured, and Dr. Work and Miss Tonkin were able to show that an extract had a definite therapeutic effect in bird malaria.

Arising out of the investigation on the chemotherapy of typhus, numbers of synthetic compounds were available for tests in other directions. Dr. Fuller found that *p*-tolylguanidine had a strong bacteriostatic action on certain bacteria, and Miss Tonkin found that this compound also had a slight true causal prophylactic action on sporozoite-induced infections of *P. gallinaceum* in chicks. Dr. King and Miss Tonkin have explored the possibilities in this discovery, and have found that *p*-anisylguanidine is the best compound of its type.

Compounds with prophylactic activity are very infrequent, but it is on record that the I.G. Farbenindustrie had such a one in " Endochin ". Dr. Walker

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Miss Stephen and Miss Tonkin have prepared and tested a number of tetrahydroacridones and related compounds which bear some relation to "Endochin," and have found compounds with a noteworthy degree of true causal prophylactic activity against sporozoite-induced malaria in chicks. Dr. Walker has also examined the possibility of converting sulphanilamide into compounds which act on bird malaria, by the introduction of basic side-chains.

Concurrently with the chemical work described above, Dr. Hawking has carried out biological investigations bearing on the general problem of the chemotherapy of malaria. In 1942 he began to cultivate *Plasmodium gallinaceum in vitro*. The forms which occur in the red blood corpuscles could not be grown for more than a few days, but the forms which occur in reticulo-endothelial cells—the exo-erythrocytic forms—could be cultivated for several months by a tissue culture technique. Chickens were infected from the cultures 89 days after the parasites had been removed from the previous host. This was the first time that a method had been described by which malaria parasites could be grown *in vitro* for more than a few days.

The new technique provides favourable opportunities for studying the morphology of the different parasitic stages, and illustrations of the various phases have been published. Although cultures could not be initiated by adding fresh sporozoites to cultures of macrophages, they could be prepared from sporozoites which had been in a chicken only for one hour, which seems too short a period to permit any fundamental change.

This technique has been applied to the cultivation of other intracellular protozoal parasites, and the exo-erythrocytic forms of *Plasmodium relictum* and of *P. lophurae* have been grown, and so have *Trypanosoma cruzi* and *Leishmania donovani*. Probably any parasite which has an intracellular cycle in a cell which can be grown in tissue culture, can be cultivated *in vitro* along these lines. When leishmania were cultivated in cells at 37°C., an unexpected development occurred after 20 days of growth; the rounded leishmania inside the cells developed into the free swimming flagellate or leptomonad form. This metamorphosis, which is known to occur in the insect vector or *in vitro* at 25°C., had not previously been observed at 37°C., and the matter required further elucidation.

The action of antimalarial drugs upon these cultures of the tissue forms of *P. gallinaceum* has been studied by Miss Tonkin. She found that sulphonamide, and certain other compounds, such as V187 and SN11437, destroyed the parasites without harming the tissue cells (except in high concentrations). On the other hand, all the well known antimalarial drugs, e.g. quinine, mepacrine, pamaquin and "Paludrine," were almost devoid of action upon the parasites in the maximum concentration tolerated by the cells. This work on the tissue forms of bird malaria has led on to a search for similar forms in mammalian malaria, and an investigation is being made of the morphology and location of *P. cynomologi* in monkeys during the incubation period following sporozoite inoculation; so far, no success has been obtained in the latter study.

Tuberculosis.—During the last year under review Dr. D'Arcy Hart has been engaged in experimental research on tuberculosis. With Mr. Glover, attempts have been made to discover individual nutrients that may be responsible for increased susceptibility of the animal host to infection.

Dr. Hart has also begun a search for antibiotics active against *M. tuberculosis*, and he is collaborating with Dr. Callow in the detailed study of one of these which shows some promise and which is derived from *B. licheniformis*.

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Endocrinology

Iodinated proteins.—Shortly before the war, Ludwig and von Mutzenbecher, in Germany, made the remarkable observation that iodination of certain proteins, particularly casein, under controlled conditions, gave products with physiological activity similar to that of the thyroid gland and from which it was possible to isolate thyroxine. Having in mind the known effect of thyroid feeding of cows in increasing the value and the fat content of the milk secreted, Dr. Young, in a report submitted jointly with Dr. S. J. Folley to the Agricultural Research Council, suggested that the possibilities of the practical application of these results should be studied. The investigation was begun in 1941 on behalf of the Agricultural Research Council by a group under the chairmanship of Dr. Harington, which studied the methods of preparation of active iodinated proteins, arranged for their large-scale production and organised the first field trials. Since Dr. Harington became Director of the Institute in 1942, his place in this work has been taken by Dr. Parkes.

The upshot of the whole investigation has been the demonstration that it is possible, by administering properly prepared iodinated protein to lactating cows, to produce a very significant increase in the quantity of milk secreted. The effect is most pronounced just after the peak of normal lactation has been reached; over periods of 6-8 weeks from this point increases of 20-25 per cent. have been obtained in the milk output of treated cows as compared with that of control animals. If the treatment is given without simultaneous food supplement the increased milk is obtained at the expense of the flesh of the animal, which consequently loses in weight and condition; these losses can be largely prevented by additional feeding in proportion to the extra milk secreted. In any case the practical application of the procedure would best be made for a period not exceeding 2 months at the time of low milk production, i.e. in the late winter; in such a case the treated animals would rapidly recover lost weight with natural feeding on the spring flush of grass.

At the time when Dr. Parkes began to take an active part in this work there was great need for a method of assaying the biological activity of preparations of iodinated protein. In the case of thyroid gland it is possible to obtain information as to the thyroxine content by a simple chemical analysis; with iodinated proteins the problem is more difficult, since they contain physiologically inactive iodine compounds which behave chemically like thyroxine. It was therefore clearly desirable to subject the preparations to biological test, and Dr. Parkes and his colleagues have examined the possibility of finding a rapid and simple method of assay.

The existing methods of assay of thyroid-active substances depended for the most part on the measurement of the effect on the metabolism of small animals; these methods were time-consuming and, for a reasonable degree of accuracy, they required the use of large numbers of animals and of complicated apparatus. Experiments carried out by Dr. Rowlands having shown that the effect of thyroid on the growth rate of thyroidectomised rats did not afford a satisfactory basis of quantitative assessment, Dr. Parkes turned his attention to the effect in accelerating the metamorphosis of tadpoles. This method of testing for thyroid activity had of course been much studied in the past; it was clear that it was the simplest available test and that it had quantitative possibilities. It suffered, however, from the great disadvantage that it was confined, by the availability of the experimental material, to a relatively short season of the year. This difficulty Dr. Parkes overcame by the use of the tadpoles of *Xenopus*, the South-African clawed toad, in which species oviposition can be induced at any desired time by administration of

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gonadotrophin. A colony of these toads has been established at the Institute, and with its aid Dr. Parkes and Dr. Deanesly have made a very large number of assays.

So far as the present problem is concerned, they were able to show good parallelism between the effects of various preparations of iodinated proteins on the speed of metamorphosis and their galactopoietic activities, so that to this extent the test fulfils all requirements. More detailed studies of the effects on metamorphosis of compounds chemically related to thyroxine make it somewhat doubtful whether the test is a specific index of the effect on the metabolism of higher animals; thus, diiodotyrosine, which is without effect on mammalian metabolism, shows definite activity in the tadpole test. This question is still being studied, and the method is also being used for the study of antithyroid substances.

Oestrogens.—As the result of studying a large number of substances with oestrogenic properties, Dr. Emmens has demonstrated that these compounds fall into two clearly defined groups, which he designates as oestrogens and pro-oestrogens. The members of the former group, which all seem to possess the phenanthrene nucleus or a chemical structure which may be supposed to simulate this nucleus, act directly; the pro-oestrogens, on the other hand, which comprise a miscellaneous group of chemical compounds, apparently give rise in the body to truly oestrogenic metabolites; their administration to animals results in the excretion of true oestrogens in the urine.

The power of synthetic oestrogens to induce lactation in virgin heifers was made the subject of extensive investigations by the Lactation Committee of the Agricultural Research Council, on which Dr. Parkes and Dr. Young both served; they both also took part in the experimental work, and, with Mr. Glover, Dr. Parkes was able to show that satisfactory lactation could be induced by a single injection of a mixture of a quickly-acting and a slowly-acting ester of stilboestrol.

Studies on fertilisation.—Dr. Rowlands has investigated the liquefying action of hyaluronidase on the gel which surrounds the unfertilised tubal ovum. Working with rabbits, he has found that the fertilising capacity of artificially inseminated sperm can be markedly increased by the addition of an extract containing hyaluronidase. The effects of various physical and chemical treatments of spermatozoa on their fertilising capacity, and on the production of abnormalities, are being further studied by Dr. Parkes.

Anterior pituitary hormones.—Up to the time when he left the Institute, Dr. Young continued his work on the analysis of the effect of the diabetogenic hormone, and on the fractionation of anterior pituitary extracts. He showed that dogs were most responsive to the effect of the diabetogenic hormone when on a diet of meat; cats also could be made diabetic, but rats were entirely resistant under all dietary conditions. Owing to the suppressive effect of oestrogens on the anterior pituitary, their administration might be expected to alleviate pituitary diabetes in the dog; this expectation was not realised in practice.

In adult dogs receiving just enough meat to maintain body weight under normal conditions, the daily administration of pituitary extract led to retention of nitrogen, and corresponding increase of body weight, preceding the onset of glycosuria. An attempt in collaboration with Dr. D. P. Cuthbertson (pp. 127 and 129) to utilise this nitrogen-retaining effect to increase the rate of healing of experimental bone fractures and skin wounds in rats was not successful, although nitrogen retention in this species was equally striking, even when the dietary source of nitrogen was a very imperfect protein.

The galactopoietic effect of anterior pituitary extract was studied in farm animals by Dr. Young in collaboration with Dr. Folley of the National

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Institute for Research in Dairying; it was found that an effect could be elicited, the response being much greater in older cows than in heifers.

Glycogenopoietic substances.—It was found by Dr. Young, working with Mr. Marks and Mr. Griffiths, that certain oestrogens induced an increased formation of glycogen in the fasting rat, resembling in this respect the hormone of the adrenal cortex. This observation was later extended to non-oestrogenic steroids and to the simpler compound 4:4′-dihydroxydiphenyl ether. In an attempt to develop this work a number of diphenylether derivatives was synthesised by Dr. Walker, but none of them proved active in increasing the liver glycogen of fasting rats or in prolonging the survival time of adrenalectomised animals.

Serum gonadotrophin.—A prolonged and systematic study of serum gonadotrophin was carried out over several years by Dr. Rimington with biological collaboration from Dr. Rowlands. The source of material was the serum of pregnant mares, and the first part of the work was directed to the working out of a simple process for the preparation of a stable extract. This was achieved, and the process, which made possible the preparation of stable material having 200-400 international units per mg. in a yield (on the laboratory scale) of over 70 per cent. of the initial activity of the serum, was made available to manufacturers, and has been used for large-scale production. Further developments in methods of purification have enabled Dr. Rimington to obtain material having as much as 12,500 international units per mg. At this high degree of purity the hormone becomes much less stable; it gives the reactions of a glycoprotein containing about 16 per cent. of hexose and 8 per cent. of amino-sugar, and in its chemical behaviour it shows some resemblances to the blood group A substance.

Biochemistry

Pigments.—Dr. Rimington has maintained his interest in porphyrins and has made several contributions to methods for their estimation. With the help of Dr. Schuster he designed a fluorescence comparator, and he has determined the *p*H : fluorescence curves for uro- and copro-porphyrins I and III over a wide range, in order to define the most suitable conditions for fluorescence measurements of these pigments. The adsorption of porphyrin from dilute acid solution upon kieselguhr has been made the basis of a convenient method of estimating uroporphyrin in pathological urine; this technique has been used for the systematic study of porphyrin excretion in a case of idiopathic porphyria. Porphyrin excretion has also been studied in connection with T.N.T. poisoning. Dr. Rimington has discovered an enzyme system in yeast press juice which is capable of synthesising a coproporphyrin from a precursor which is present in extracts of fresh yeast but is not identical with haematin or with any known porphyrin.

By examination of urine from cases of " crush injury " sustained in air-raids (pp. 51-2) Dr. Rimington was able to show that the pigment excreted differed spectroscopically from haemoglobin; subsequently it was identified as the muscle pigment myoglobin (myohaemoglobin).

Studies of amino-acids.—A systematic investigation aiming at the closer analysis of the effects of dietary deficiency of individual amino-acids, and the identification of the biochemical lesions produced by such deficiencies, has been undertaken by Dr. Neuberger. The programme has necessitated the expenditure of much time in the preparation of the pure amino-acids necessary for the rigid control of dietary conditions; in the course of this work new and convenient methods were developed. With Mr. Webster, Dr. Neuberger has shown that lysine is necessary not only for growth in the rat, as had previously been recognised, but also for tissue maintenance in the adult animal.

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He has also made the important observation that lysine is essential for normal haemopoiesis in the growing animal. The question of histidine deficiency has been studied, also with Mr. Webster, and it has been shown that the rat cannot synthesise the iminazole ring of histidine from potential precursors, and that it cannot utilise thiolhistidine in place of histidine itself. The pathological effects of histidine deficiency have been examined and, in an attempt to analyse their nature, attention has been paid to concomitant changes in the muscular content of carnosine and anserine. Dr. Neuberger has collaborated with Professor Himsworth and Dr. L. E. Glynn of University College Hospital in a study of the metabolic changes and hepatic lesions resulting from deficiency of sulphur-containing amino-acids; the result of this work has been to show that the effects are due to deficiency of cystine rather than of methionine.

In parallel with his nutritional studies Dr. Neuberger has worked on the chemistry of certain amino-acids. As part of a general investigation of the action of formaldehyde on proteins he has examined the reaction of this compound with histidine, making the interesting observation that an early product of the interaction is a tetrahydropyridine derivative. He has also studied the stereochemistry of hydroxyproline, showing that the carbon atom carrying the hydroxyl group has the *d*-configuration in the acid as it occurs in protein, and the *l*-configuration in *allo*hydroxyproline.

Dr. Harington and Mrs. Pitt Rivers have synthesised the hitherto unknown dipeptides of cystine and tyrosine, and have examined the action of pepsin on them. Both the peptides are hydrolysed to some extent by this enzyme, thus affording the first instance of dipeptides being so attacked. Hydrolysis is favoured by acylation of the amino group and by the reduction of the cystine residue to cysteine; the latter observation is of interest in connection with the mode of action of pepsin on proteins, and the results in general have a bearing on the theory of the mechanism of peptic hydrolysis.

Biosynthesis of thyroxine.—The studies of physiologically active iodinated proteins, which have been mentioned on p. 219, caused a revival of interest in the mechanism of the biological formation of thyroxine. At the time of his early work on the structure of thyroxine Dr. Harington had suggested that the biosynthesis probably occurred through the oxidative coupling of two molecules of di-iodotyrosine, but no direct chemical evidence of the possibility of such a transformation had been forthcoming. It seemed highly probable that the thyroxine formed during iodination of proteins originated in this manner, and this was made still more likely by the claim of von Mutzenbecher that traces of thyroxine were formed when di-iodotyrosine was incubated in alkaline solution. The problem was taken up by Dr Harington and Mrs. Pitt Rivers, who have shown that it is in fact possible to obtain significant yields of thyroxine by the oxidation of di-iodotyrosine in alkaline solution with hydrogen peroxide; of perhaps greater significance is the evidence produced that the effective oxidising agent in this reaction is iodine itself, for this makes it possible to form a picture, on the basis of actual chemical experiments, of a process of biosynthesis of thyroxine in which the only biochemical step required is the liberation of iodine from iodide by an enzymic oxidising system. The implications of this for the theory of thyroid function, and the theoretical basis of the chemical transformation of di-iodotyrosine into thyroxine, have been discussed in publications by Dr. Harington.

Immunology

Tetanus.—In 1940-41 workers at the Institute were offered active immunisation against tetanus. About 100 persons availed themselves of this offer and received two spaced injections of tetanus toxoid. A follow-up of this work

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was conducted by Dr. Evans with the object of studying the persistence of immunity. The results showed that a third dose of toxoid, given a year after the initial two doses, produced a concentration of circulating tetanus antitoxin which persisted for at least 18 months at a much ligher level than that resulting from two doses only. In relation to this study, and with a view to assessing the probable immune response in man under unfavourable conditions, an investigation was made with Sir Percival and Lady Hartley of the response of guinea-pigs to antigenic stimulus under conditions of (*a*) reduced diet, (*b*) exposure to cold, and (*c*) non-specific infection. None of these factors was found to have a significantly adverse effect on the immune response.

Diphtheria.—Sir Percival Hartley has continued his studies of diphtheria antitoxin and has found that in the pregnant guinea-pig homologous antitoxin passes the placental barrier, whilst antitoxin made in the horse does so much less readily. Moreover, antitoxin in the form of natural serum passes the placental barrier more easily than does antitoxin refined by the modern process of peptic digestion. Homologous antitoxin (particularly when in the form of natural serum) is retained in the circulation of the guinea-pig much longer than heterologous antitoxin prepared in the horse; on the other hand, the homologous antitoxin offers no superiority for the treatment or control of diphtheritic toxaemia in the guinea-pig.

Studies, undertaken for the Council's Committee on Preventive Medicine, of the antitoxin content of the serum in cases of diphtheria arising in immunised persons have been continued by Sir Percival Hartley over several years; this investigation, made in collaboration with the Medical Officers of Health for Newcastle-on-Tyne and Gateshead, is now complete and the results are being prepared for publication.

Gas gangrene.—Dr. Evans has made a systematic immunological study of experimental infections produced in guinea-pigs with various strains of *Cl. welchii.* Each of these strains was examined for its power to produce α-toxin, θ-haemolysin and hyaluronidase, and also for its ability to cause fatal infection in guinea-pigs. The virulence for these animals was consistently found to be correlated with the power to produce α-toxin *in vitro,* but bore no relationship to the power to produce θ-haemolysin or hyaluronidase. The general conclusion is that α-toxin is the most important agent in the infection, and α -antitoxin therefore the essential factor in the antiserum. Anticollagenase was found to be without effect on the infective process, either by itself or in conjunction with α-antitoxin. If specific antitoxin be given early in the disease to guinea-pigs infected with *Cl. welchii, Cl. oedematiens* or *Cl. septicum,* it will produce a notable improvement in the clinical condition and will prolong life considerably; if the toxaemia is controlled for long enough in this way, the animal may rid itself completely of the specific organism.

The Vibrios.—In addition to his work for the Emergency Public Health Laboratory Service (p. 164 *et seq.*), for which he carried on numerous special investigations and to which he acted as consultant on pathogenic intestinal bacteria, Mr. Bruce White continued his studies of vibrios during the early part of the war. He has obtained the protein-free carbohydrate haptene of the " rough " cholera vibrio in a state of approximate purity, and has started a systematic investigation of the relationship of antigenic variations to morphological changes in the vibrio, and of the disposition of individual antigenic factors in the various elements composing the culture. In the first phase of this work Mr. Bruce White has studied the " spherical bodies "

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and radially arranged cell aggregates which are formed in vibrio cultures, applying to the investigation newly developed and powerful methods of differential staining.

Anthrax.—Later in the war Mr. Bruce White turned his attention to the problem of immunity against anthrax. Previous work had failed to reveal any method of immunising animals against anthrax with a non-living vaccine, except for the observation of Bail on the immunising power of the toluene-treated spore-free oedema fluid from infected animals; it was further known that virulence in an anthrax strain requires retention of the power of capsulation *in vivo*, although capsulation in culture does not necessarily imply virulence. Starting from this point, cultures of a virulent strain of anthrax were exposed to complement-activated Sclavo's anti-anthrax serum, the mixture was plated out and aberrant colonies were selected. Non-sporing strains thus obtained were subjected to a second selective treatment with another anti-anthrax serum, and there was eventually isolated a strain which was highly capsulate in ordinary culture; this strain, although of reduced pathogenicity, was not avirulent; being non-sporing, it could be killed by heat at 50-60°C. or by exposure to toluene or chloroform, to form vaccines. Treatment with such vaccines gave some measure of protection to guinea-pigs against infection with the fully virulent strain. Survival or prolongation of life was observed after challenge with 10-100 M.L.D., but not after more than 500 M.L.D.; moreover, no protection was afforded against respiratory infection with anthrax spores. The suggestion, derived from earlier work, that the full immunising capacity of anthrax strains was developed only in the course of growth *in vivo* led to experiments in which the non-sporing strain was cultivated in whole blood: protection experiments in animals show that vaccines prepared by treatment of such blood-cultures with toluene have a significant degree of immunising power.

In the course of this work improved methods have been developed for the isolation of the capsular material of *B. anthracis*, and studies have been made of morphological variations of the organism which occur under different cultural conditions.

Typhoid fever.—Dr. A. Felix, serving as a member of the Emergency Public Health Laboratory Service, worked in the National Institute from May, 1941, to November, 1942. During this period he continued his work on the preparation of typhoid-paratyphoid vaccine with a high content of Vi antigen. He also studied the application of the Vi agglutination reaction to the detection of chronic paratyphoid B carriers and, with the assistance of Miss B. R. Callow, demonstrated the usefulness of Vi bacteriophage in the typing of paratyphoid B. bacilli.

Antigenic properties of simple chemical compounds.—Because of the trouble which was being experienced in certain ordnance factories from dermatitis caused by tetryl, an investigation of the sensitising properties of this compound was undertaken by Dr. Gell together with Dr. Harington and Mrs. Pitt Rivers. The mechanism of action of tetryl in this respect became clear when it was shown that it reacted readily with amino-groups (and therefore with proteins) to form *N*-trinitrophenyl (or "picryl") derivatives with specific immunological properties. A study was made of the relationship of systemic immunisation to skin sensitivity, with negative results, the two processes appearing to be entirely independent. This work led to a general research by Dr. Harington, Dr. Gell and Mrs. Pitt Rivers into the antigenic properties of simple chemical compounds.

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Biophysics and Physical Chemistry

During the period under review the application of new physical methods to the general research work of the Institute has greatly increased in scope and importance. Outstanding additions to equipment have been an air-driven high-speed centrifuge, an electron microscope and a Tiselius electrophoresis apparatus. These apparatus are in regular use, and they have been employed for the most part in collaborative researches. Thus, Dr. Elford has used the centrifuge in successful attempts with Mrs. Hamilton to prepare purified and highly concentrated suspensions of influenza virus for the purpose of examination with the electron microscope.

Dr. Bunn, working under the general supervision of Dr. McFarlane, has given much help to other members of the staff with the electrophoresis apparatus. He has himself studied the electrophoresis of purified preparations of taka-diastase made by Dr. Rimington. Dr. Bunn has also collaborated with Dr. Fulton in physical methods of investigating rickettsiae and the psittacosis-lymphogranuloma group of organisms.

Dr. McFarlane, who was appointed to the staff in 1944, has resumed his earlier work on vaccinia virus. He has studied it with the aid of the electron microscope and has also investigated its desiccation at very low temperatures; this method of low temperature drying is being applied, in collaboration with Dr. Parkes, to human spermatozoa.

The electron microscope was set up in the Institute in 1943 by Dr. McFarlane and Mr. Smiles, with valuable help from the staff of the National Physical Laboratory; it has since been used extensively in the study of bacteria and viruses. Mr. Smiles has investigated the effects on biological material of the drying which necessarily precedes electron microscopic examination, and has made contributions to the technique of preparing objects for examination.

Mr. Smiles has also continued his work on ultra-violet microscopy, and has collaborated in studies of pleuropneumonia-like organisms (with Miss E. Klieneberger, of the Lister Institute, and with Dr. Andrewes), of chromosome structure (with Miss I. Manton of Manchester University), of mammalian ova (with Dr. E. C. Amoroso of the Royal Veterinary College, London) and of the action of penicillin on bacteria (with Dr. Elford). In the course of this work a useful technical advance has been made in regard to the preparation of selected material for ultra-violet microscopy: after location of the desired objects on a glass slide by ordinary microscopy, the specimen is treated with collodion solution; after drying, the collodion film with the specimen embedded in it can be stripped and transferred to a quartz slide, to which it adheres when the collodion has been dissolved away. This technique can also be used in electron microscopy.

Dr. Elford, in the early part of the war, collaborated on the physico-chemical side in the work on bactericidal aerosols to which reference has been made elsewhere in this Report; his experiments related particularly to hypochlorous acid and ozone. Later he studied and defined the physical factors affecting the stability of rickettsial suspensions, and also the conditions necessary for reproducible staining of rickettsiae by the Machiavello method. He made a comparative study of various strains of typhus by the filtration technique; this indicated a lack of homogeneity in the size of the rickettsiae of any one strain, the smallest being 0.4 to 0.6 μ, but no conspicuous size differences were observed between the different strains. Continuing his studies of bacteriophage, Dr. Elford has examined the combined action of bacteriophage and penicillin on *Staph. aureus* and other organisms; he finds that the two agents behave synergistically.

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A physico-chemical investigation which deserves mention is the work which Dr. Neuberger undertook on the electrometric titration of penicillin. At the time when this was done, pure penicillin was still a rarity and could be made available in quantities of milligrammes only. With the aid of Dr. McFarlane and Dr. Schuster, a micro-electrometric titration apparatus was designed, and this enabled Dr. Neuberger to carry out a series of titrations of the small amount of penicillin which could be obtained. Titrations were performed at different temperatures and in different solvents; from the effects of these variations in conditions on the apparent dissociation constants of the titratable groups of penicillin, Dr. Neuberger was able to draw theoretical conclusions as to the nature of these groups, which were recognised as constituting a significant contribution to the problem of the structure of penicillin (p. 90).

Prostistology

During the war Dr. Dobell continued his researches on the intestinal amoebae of man. He has completed his study of the life-history of *Endolimax nana,* and has made much progress with that of *Iodamoeba,* which is the last of the known amoebae living naturally in the human intestine to await detailed description; he has been able to cultivate this organism *in vitro* for the first time. Dr. Dobell has also succeeded to a considerable extent in the difficult task of defining precisely the conditions required for the cultivation *in vitro* of *E. histolytica;* this work, which has already led to the cultivation of the amoeba together with only one known bacterium, is paving the way to the important objective of the production of pure *E. histolytica* cultures. On various occasions during the war Dr. Dobell was able to give expert protistological advice to physicians having charge of cases of amoebic dysentery.

Library

Reference has been made on pp. 206-7 to the retirement of Miss K. Baverstock from the post of librarian, and to the appointment of Miss E. Wigmore as her successor; the subsequent appointment of Miss H. Clark as Assistant Librarian has also been mentioned.

During the years 1939-45, 2,255 bound volumes (1,187 periodicals, 1,068 books) were added to the library; of these, 170 volumes were received as gifts. The Council wish to record their thanks to all who have contributed to the usefulness of the library by presenting books and periodicals. The total number of volumes in the library now exceeds 18,000. In addition to books and journals, two valuable reprint collections were received as gifts from Sir Edward Mellanby and Dr. Harington. The reprints in these collections, as well as 5,000 other reprints, have been catalogued and made available for use.

The impact of the war was soon visible in the periodical collection. Many American journals were lost by enemy action, and journals from enemy and enemy-occupied countries ceased to be received. All the lost issues of American journals were subsequently replaced, and, through H.M. Stationery Office, a large number of the foreign journals, urgently needed, were in due course obtained.

Dr. Schuster provided the library with an ingenious microfilm reader of his own design, which has enabled readers to have access to material available only in microfilm.

Because the *Quarterly Cumulative Index Medicus* was at that time almost a year behind in publication, a card index (author and subject) to current

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periodical literature was started in 1942. This has proved of service to workers at the Institute and will be continued so long as there is need for it.

As in previous years, approved persons interested in medical research have been permitted to consult books and periodicals in the library by arrangement with the librarian.

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XII

THE PREPARATION AND MAINTENANCE OF BIOLOGICAL STANDARDS

Work upon Biological Standards at the National Institute for Medical Research

(*For Staff in September, 1945, see p. 203.*)

The outbreak of war in 1939 was a threat to the activities, and even the continued existence, of the Permanent Standards Commission of the League of Nations—the body which had hitherto co-ordinated the arrangements made in Great Britain and other countries for the preparation, maintenance and issue of international standards of purity and activity for many important medicaments, including various antitoxins, hormones, vitamins and essential drugs. Until then, the Commission had been available to advise when help or guidance was required in regard to particular international standards, and to sanction any necessary changes; after the declaration of war, this solid basis for the standards work virtually disappeared, and the difficulties increased as the German domination of Europe extended.

In the years immediately preceding the war, National Control Centres for the distribution of international standards, and in some cases also for the local preparation of standards, had been established in different countries. When war seemed imminent, the great practical utility of these Centres was emphasised. In the spring of 1939, on the Council's initiative, large stocks of all the international standards maintained at Hampstead, estimated to be sufficient to last for several years, were despatched to each of the National Control Centres; acknowledgment of their safe arrival was received at Hampstead, and there is good reason to believe that, throughout the war, most countries were adequately provided with the international standards for drugs, hormones and vitamins. As an additional security, in 1941, 1942 and 1943 six separate consignments of the international standards were sent to Dr. R. Gautier at Geneva; in this way, supplementary stocks were available in Geneva to meet any shortages which might occur in countries having no direct access to supplies from Hampstead.

Another serious feature of the situation arising from the war was that it was in London that the material standards for drugs, hormones and vitamins had been deposited: these standards had been established as the result of the co-operative investigations and united endeavours, over nearly twenty years, of research workers in many different countries. The standards did not belong to one nation but, through the Health Organisation of the League, to all the nations in common. Great Britain was thus the custodian of important international property, and to safeguard the standards from destruction by enemy action, they were dispersed to several depots throughout England.

The seizure of Denmark by Germany in April, 1940, created further difficulties: some of the Allied nations, as well as the countries not yet occupied by Germany, were now unable to obtain supplies of the standards for antitoxins, antisera and tuberculin. This was particularly serious, because during wartime there is a special demand for tetanus and gas gangrene antitoxins for the wounded. Fortunately, large stocks of all these serological standards, or their exact equivalents, are normally maintained at Hampstead in order to fulfil the obligations of the Council to the Ministry of Health in respect of the Therapeutic Substances Act, to the British Pharmacopoeia

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Commission, and to the governments of the Overseas Dominions. Accordingly, when a request from the League of Nations was received for the provision of these antitoxin and antiserum standards to countries which could no longer obtain their supplies from Copenhagen, it was possible to comply with this request from Hampstead, and thus this valuable international service was maintained throughout the war.

In the summer of 1940, under the threat of invasion, further precautions seemed desirable to preserve the international biological standards from loss and, with them, the international units. Accordingly, a stock of the antitoxin and antiserum standards, sufficient to permit the reproduction of the international units in case of need, was transferred to Canada, cold storage and laboratory accommodation being generously provided by the Department of Pensions and National Health, Ottawa. In addition, a fully detailed description of the laboratory and other procedures which would be necessary in order to replace these antitoxin and antiserum standards, was prepared at Hampstead, and copies of this document were deposited not only at the Council's central office and at the National Institute for Medical Research in London, but also with the International Health Board of the Rockefeller Foundation in New York, and with the Departments of Pensions and National Health, Ottawa.

It is satisfactory to record that progress in the field of international biological standardisation did not cease with the coming of war, despite the fact that the international body, under which this work is normally carried out, had practically ceased to exist, and had certainly ceased to function. The war created new fields for the assay of substances by biological methods and increased directly, and to a notable degree, the call on many of the standards maintained by the Council at Hampstead.

New Standards

Three new biological standards have been provided and made available from Hampstead during the war; these are for vitamin E, heparin and penicillin.

Vitamin E.—Through the generosity of Messrs. Hoffman-La Roche of Basle, 100 g. of pure synthetic racemic α-tocopheryl acetate were placed, before the war, at the disposal of the International Vitamin Standardisation Conference for investigation, particularly in regard to its suitability as an International Standard for vitamin E. This material was received at Hampstead in February, 1939, and after chemical, physical and biological investigations had been promoted by the Vitamin E Sub-Committee of the Accessory Food Factors Committee (p. 107), its adoption as a standard was recommended, in 1940, by the members of the International Vitamin Standardisation Conference who were available in Great Britain. Acting on behalf of the Health Organisation of the League of Nations, the Department of Biological Standards at Hampstead undertook the care and distribution of this material, which is issued as a standard solution in olive oil.

Heparin.—The increasing use of heparin as an anticoagulant, due largely to improvement in the methods of its isolation from natural sources, made the question of its standardisation and assay one of urgent practical importance. Owing to the war, the task of selecting a suitable preparation as a standard, and of organising its international use, could not be undertaken by the Permanent Commission on Biological Standardisation of the Health Organisation of the League of Nations. Initiative in this matter was, therefore, taken by the Department of Biological Standards at Hampstead.

Through the kindness of Professor C. H. Best, a specimen of heparin was prepared by the Connaught Laboratories of the University of Toronto, and made available for standardisation purposes. The material (85 g. of air-dried

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sodium salt on receipt) was dried and stored under the routine conditions adopted by the Department of Biological Standards. Investigations of stability were made, and a detailed study of the method of biological assay was carried out by Dr. F. C. MacIntosh. Before its final drying, the standard material was compared in two laboratories with the provisional British Standard for heparin. Finally it was issued as a provisional International Standard, the unit being defined as the activity contained in 1/130 mg. of the standard dry powder. This unit is very close to the "Toronto unit" originally proposed by Murray and Best.

Penicillin.—Perhaps the most important task which has fallen to the lot of the Department of Biological Standards during the war has been work in connection with the establishment of an International Standard for penicillin. The urgent need of such a standard became evident with the increase in production and use of penicillin which occurred in 1944. Again the initiative was taken by the Department of Biological Standards and by then, owing to the improved war situation, it was found possible to revive the Permanent Standards Commission and to organise an International Conference to deal with the matter. This conference was held in London, in October, 1944, under the chairmanship of Sir Henry Dale, and was attended by delegates from Great Britain, the United States, France, Australia and Canada. Preparatory work on the dispensing of samples for assay, and in the arrangement of preliminary comparative investigations in eight different laboratories in Great Britain, the United States and Canada, was undertaken by the Department of Biological Standards, the reports of this work forming the basis of the discussions of the Conference. Agreement was reached without difficulty to the adoption of pure crystalline sodium penicillin II as the International Standard, and recommendations were made on points of nomenclature, and on the establishment of an International Working Standard for penicillin, consisting of a partly purified calcium salt. The material for the International Standard consisted of samples of pure sodium penicillin II (some 8 g. in all), contributed by various commercial firms in the United States, and by Imperial Chemical (Pharmaceuticals), Ltd., in Britain. These samples were assembled in the Northern Regional Laboratory, Peoria, U.S.A., and there recrystallised together by Dr. R. D. Coghill; after careful determination of physical constants, the material was then sent to Hampstead, where it has been dispensed and stored in the usual way. The unit of penicillin was defined by the Conference as being the activity contained in 1/1,666 mg. of the International Standard, the value of this unit being very close to that of the "Oxford unit" originally proposed by Sir Howard Florey and his co-workers (p. 81).

Pending the establishment of the International Standard, and for some time after its adoption, penicillin in this country was standardised against a Provisional British Standard, consisting of a preparation of partly purified penicillin calcium salt, supplied jointly by the Therapeutic Research Corporation and Imperial Chemical (Pharmaceuticals), Ltd. This material is now being replaced by a British National Standard of crystalline sodium penicillin II, 30 g. of which were generously presented for this purpose by the Glaxo Laboratories, Ltd.

During 1944-45, the Department of Biological Standards assisted the Ministry of Supply by carrying out assays of all manufacturers' batches of penicillin. This work, involving the examination of some 1,000 samples of penicillin, was undertaken by Mr. P. Bruce White.

Anterior pituitary gland.—During the war, effect was given to the recommendation of the Third International Conference on the Standardisation of Hormones, held in Geneva in August, 1938, that a standard preparation

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of the whole anterior pituitary gland should be established and maintained. Through the courtesy of Mr. J. B. Bradshaw, 4.5 kg. of desiccated ox anterior pituitary gland were made available for this purpose by Armour and Company, Inc., Chicago. The material was received at Hampstead and dispensed in the usual way. Assays were made of its gonadotrophic, prolactic and thyrotrophic activities.

Replacement Standards

During the war, the necessity arose for the preparation of several replacement standards.

Androsterone.—The supply of the International Standard for this hormone became exhausted in 1939. Replacement was made possible by the generous gift of 30 g. of androsterone by Dr. K. Miescher on behalf of Ciba, Basle. This material was found to conform in physical properties to the requirements laid down at the Second International Conference on the Standardisation of Sex Hormones, and has been adopted as the Second International Standard for Male Hormone.

Vitamin C.—With the aid of two gifts of 250 g. of pure ascorbic acid from Dr. F. H. Carr, of British Drug Houses, Ltd., and Dr. F. Bergel, of Roche Products, Ltd., a second (replacement) International Standard for vitamin C has been established.

Vitamin A.—Since the stocks of the original preparation of β-carotene, which constitutes the International Standard for vitamin A, were nearing exhaustion, steps had to be taken for its replacement. A generous gift of 20 g. of pure β-carotene was made by Lever Brothers, Ltd., for this purpose. Careful spectrophotometric comparison of this material with the original International Standard (supplied by Professor P. Karrer, of Zurich) showed complete identity, so that the new preparation could be recommended for adoption as the second (replacement) International Standard for vitamin A.

Gas gangrene antitoxins.—The increased demand for serological standards from the Department of Biological Standards, at Hampstead, as a result of the German occupation of Denmark in 1940, was particularly heavy in respect of the standards for the gas gangrene antitoxins, and it became necessary to make replacement preparations. Material for these replacements was supplied by the Wellcome Foundation through Mr. A. T. Glenny of the Wellcome Physiological Research Laboratories, Beckenham, who gave much assistance in the selection of samples of the antitoxins as closely as possible resembling the International Standards in properties. The three selected samples of *Cl. perfringens* (*Cl. welchii*), *Cl. oedematiens* and *Cl. septicum* antitoxins, respectively, were converted into the dry stable condition by the usual technique. The dry preparations were carefully assayed in terms of the corresponding International Standards in three different Laboratories, and have taken their place as the British National Standards for the respective antitoxins.

(For publications see list on pp. 227-241.)

The National Collection of Type Cultures of Micro-organisms

Staff (September, 1945):—

R. St. John-Brooks, M.D. (*Curator*).

Mabel Rhodes (*Assistant Curator*).

Rosamund E. E. Barnes, B.Sc.

At the time when the war began, the Curator of the Collection, Dr. R. St. John-Brooks, was in the United States attending the Third International Congress for Microbiology, in which he served in a number of official

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capacities; the task of removing the Collection from the Chelsea premises of the Lister Institute to a place of greater safety, outside London, fell, therefore, to the Assistant Curator, Miss M. Rhodes. Thanks to the detailed arrangements which had been made many months before the outbreak of hostilities, the work of transferring the Collection to its wartime home at the Lister Institute, Elstree, Herts., was completed with minimal delay.

Owing to the very limited space originally available for the Collection at Elstree, work was at first carried on under conditions of great difficulty; towards the end of the war, however, improved quarters were provided. The fall in the demand for type cultures in the early part of the war, owing to the severance of many overseas contacts, was partly compensated later by an increased demand from British workers and from workers in Allied countries—especially the United States, with which an active exchange of information and of material was maintained throughout the war period. This was greatly facilitated through the help given by the representatives in London of the United States Office of Scientific Research and Development.

The number of cultures despatched from the Collection in a full year, before the war, amounted to over 6,000. This fell to between 3,500 and 4,000 in the early years of the war, but rose again to over 5,000 during the year 1944-45. The number of cultures lodged for conservation fell from about 400 a year to an average of about 200. These were of the customary varied nature and significance—medical, veterinary, agricultural and industrial. Among the material conserved was a number of strains of special interest in the production of antibiotic substances, such as penicillin, streptomycin, streptothricin, patulin and gramicidin; there was also a series of micro-organisms concerned in the biological assay of vitamins and other substances. Among other notable additions to the Collection was a set of type cultures of pathogenic fungi of medical interest, which was deposited by Dr. Norman Conant and his colleagues of the Duke University, North Carolina, U.S.A. These were received about the time when the Council appointed a Committee on Research in Medical Mycology under the Chairmanship of Dr. J. T. Duncan, of which Dr. St. John-Brooks was Secretary (p. 424). Since then, the staff of the Collection have co-operated increasingly with American mycologists in this important field. Some other organisms of particular interest, lodged during this period, were *Mycobacterium muris*, isolated from voles (p. 70), *Trichomonas foetus*, a cause of abortion in cattle, a strain of *Torulopsis utilis* var. *major* used in protein synthesis, and some bacterial strains used in sulphonamide testing.

Dr. St. John-Brooks revisited America in 1941-1942 to work in Washington as the guest of the American Type Culture Collection. While in the United States, he visited the Iowa State College and carried out with Dr. R. E. Buchanan a revision, sponsored by the International Association of Microbiologists, of the proposed International Rules of Bacteriological Nomenclature; he also discussed international relations as affecting type culture collections. With similar questions in mind, a group of Swiss microbiologists, under the leadership of Professor Paul Hauduroy, recently convened a commission at Lausanne, to discuss international reciprocity in microbiological matters and to attempt to integrate the work of the various type culture collections, by means of exchange of information and material. Dr. St. John-Brooks attended the sessions of this conference and helped to draw up its resolutions. A *Centre de Collection de Types Microbiens* has now been established at Lausanne, and various sub-committees have been appointed to deal with different aspects of microbiology.

It has become increasingly evident that the best method of conserving bacteria in an unaltered condition, over long periods of time, is by means of

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one of the various freeze-drying methods at present in use. The "snap-freeze" method, which is now applied to all bacteria conserved in the National Collection, is also applicable to the conservation of many types of fungal spores, and is of great importance in the conservation of species of interest in antibiotic research. Cultures of bacteria conserved in the National Collection of Type Cultures, and desiccated as long ago as 1934, were found in 1945 to be still viable.

R. St. John-Brooks and M. Rhodes—
Taxonomy of the Proteus group. *Proc. 3rd Internat. Congress for Microbiology, New York*, 1939, p. 67.

R. St. John-Brooks—
The National Collection of Type Cultures. *Brit. med. Bull.*, 1944, **2**, 284.

The Standards Laboratory for Serological Reagents

Staff (*September*, 1945):—

Lieut.-Colonel R. F. Bridges, M.B., R.A.M.C. (*ret.*)

Edith F. Stubington, B.Sc.

During the war the Standards Laboratory was maintained by the Council in the School of Pathology at Oxford for the supply of suspensions and sera for the diagnosis of enteric, dysenteric, typhus, brucella and meningococcal infections. The output of these materials was much increased to meet the demands of the Emergency Public Health Laboratory Service (p. 164). Large supplies were dispatched to laboratories under the control of the Royal Navy and the Royal Air Force, both at home and abroad; and consignments were delivered to units of the United States Army, and to the British Council for transmission to Jugoslavia and China.

As a result of publications by Dr. A. Felix and others on the Vi antigen of *Bact. typhosum*, many applications were made to the Standards Laboratory for a suitable suspension for the Vi test, which had been found to be of great value in the examination and discovery of typhoid carriers. Much of the early work on this antigen had been carried out with living suspensions, which were obviously unsuitable for distribution. After some research in the Standards Laboratory, it was found possible to produce a killed and preserved suspension capable of retaining its sensitivity over a reasonable period. Large quantities of this material were manufactured and supplied to laboratories. At the same time a short note was printed and distributed on the technique recommended, indicating, also, the significance of the results which might be obtained.

Researches by Brigadier J. S. K. Boyd on the antigenic structure of the Flexner group of dysentery bacilli were of particular importance to the Standards Laboratory, since they materially affected the question of agglutinability standards. These matters were investigated, and changes were made where necessary. At the same time several other organisms, which were known to be causes of bacillary dysentery, were added to the list of those from which suspensions and sera were prepared in the laboratory for issue on request. A pamphlet on the subject was published and distributed.

During the war a number of Salmonella food-poisoning organisms of types which had not previously been found in Great Britain, were isolated in this country. The polyvalent diagnostic serum was re-organized to include these strains, and antisera for a number of special types were also provided. A paper on the use of these sera was written in conjunction with Dr. Joan Taylor, of the Salmonella Reference Laboratory, Oxford (p. 169).

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Reports from the Middle East showed that some of the suspensions issued for use in the Weil-Felix test for typhus were not sufficiently stable to withstand the effects of long storage and hot climate. This was especially so in the case of *Proteus XK*, which is used for the diagnosis of scrub typhus, prevalent in Malaya and Burma and other countries in the Far East, and of Japanese tsutsugamushi fever. The matter was investigated, and some alterations in technique were introduced which proved to be effective in rendering the suspension more stable.

R. F. BRIDGES—
Note on the preparation of suspensions for the Weil-Felix test. *Trans. R. Soc. Trop. Med. Hyg.*, 1944, **37**, 343.

R. F. BRIDGES and J. TAYLOR—
Note on the constitution and use of Salmonella agglutinating sera supplied by the Standards Laboratory, Oxford. *Mon. Bull. Min. Hlth, Lond.*, 1944, **3**, 177.

XIII

EXTERNAL RESEARCH ESTABLISHMENTS AND SCIENTIFIC STAFF

In this section an account will be given of some of the work done during the war years in the Council's research establishments other than the National Institute for Medical Research, and by certain members of their scientific staff attached to academic and other institutions. The number of the Council's permanent or semi-permanent research establishments was increased during the period covered, by the setting up of an Otological Research Unit at the National Hospital for Nervous Diseases, London; a Burns Research Unit, initially at the Royal Infirmary, Glasgow, and subsequently at the Birmingham Accident Hospital and Rehabilitation Centre; a Radiotherapeutic Research Unit at the Hammersmith Hospital, London; a Department of Experimental Medicine at Cambridge; a Human Nutrition Research Unit at the National Hospital for Nervous Diseases, London; a Cell Metabolism Research Unit at Sheffield; a Department of Research in Industrial Medicine at the London Hospital; and a Research Unit in Applied Psychology at Cambridge. Several other research units with important long-term programmes have been established by the Council since the war ended, and some of these have been mentioned in the introductory sections; since, however, their work began after the period covered, it is not reported here.

In addition to their permanent and semi-permanent establishments, the Council during the war years organised a number of temporary units and other research groups for studies, either in this country or overseas, of problems with a special and immediate bearing on the war effort. The work of the groups sent overseas has been noticed in the appropriate introductory sections. A very important example of a temporary research establishment in this country was the Council's Physiological Laboratory set up in the Armoured Fighting Vehicle Training School at Lulworth (p. 140) in relation to the work of the Military Personnel Research Committee; another was the Wound Infection Research Unit established at the Birmingham Accident Hospital and Rehabilitation Centre (p. 266). The work of the team at Lulworth has been reported in some detail on pp. 140-147 and need not be recapitulated here; among other *ad hoc* research groups working in the United Kingdom whose studies have been noticed earlier in this Report were the Jaundice Research Team (p. 66), the " Mass Radiography " Unit (p. 69), and the team under

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the direction of Dr. Russell Fraser which investigated the problem of neurosis in industry (p. 157). Similarly, the principal wartime research work of some individual members of the Council's permanent or temporary scientific staff has been covered in earlier sections; cross-references, with lists of publications, are given in the following pages where necessary.

Apart from purely research establishments, most of the organisations set up by the Council as part of the Emergency Services (p. 160) also undertook investigational work. Thus much fruitful research bearing particularly on problems of transfusion was carried out by the staffs of the London Blood Supply Depots, and by the Serum Drying and Blood Grouping Units at Cambridge. Short accounts of these studies have been given on pp. 188-195 above. Research publications from the centres in question are listed on pp. 343 and 406-410.

Some of the research work carried out by members of the staff of the Emergency Public Health Laboratory Service, directed by the Council for the Ministry of Health, is briefly reviewed in the introductory section dealing with that Service (p. 170). A list of wartime publications by members of the Service and their collaborators is given in Appendix D (p. 410).

RESEARCH UNITS AND ESTABLISHMENTS

Clinical Research

The Department of Clinical Research, University College Hospital, London

Staff:—

Sir Thomas Lewis, C.B.E., M.D., F.R.C.P., F.R.S. (*Director till March, 1945*)

E. E. Pochin, M.D., F.R.C.P.

Attached worker:—

J. R. Squire, M.B., M.R.C.P. (*till May, 1942*)

The Department sustained immeasurable loss by the death in March, 1945, of Sir Thomas Lewis, who had directed its work since its inception as the Cardiac Department in 1919.

The post of Director is permanently endowed by the Rockefeller Foundation, but the Department is otherwise staffed and supported by the Council.

At the outbreak of war, the research programme of the Department was severely curtailed, members of the staff taking up work in various London and other hospitals in connection with the Ministry of Health Emergency Medical Service scheme in preparation for air-raids. Dr. Pochin was enabled to resume his research later in September, 1939, working temporarily at the National Institute for Medical Research; subsequently, in 1940, work was initiated in the Department of Clinical Research in relation to the programme of the Committee on Traumatic Shock (p. 51). With Professor C. R. Harington, then of the Department of Chemical Pathology, University College Hospital Medical School, Dr. Pochin and Dr. Squire developed a simplified method of estimating blood volume by means of the dye Evans' Blue (T.1824). The method depended on extracting the dye from plasma samples into acid butyl alcohol. It allowed determinations to be made without the use of complicated apparatus such as recording spectrophotometers, and its results were not vitiated by the presence of lipaemia, or of moderate haemolysis, such as might be expected in human subjects following trauma; it was tested on normal volunteers and was subsequently used in estimating blood volumes in air-raid casualties.

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Dr. Squire devised an instrument for measuring the quantity of blood and its degree of oxygenation in the skin. Clinical studies in cases of shock following street accidents and surgical procedures were carried out with the aid of this device.

Dr. Pochin continued his work on the ocular signs of Graves's disease by investigating the protrusion of the eyes in patients so affected. With Mr. F. F. Rundle, who was working at the Westminster Hospital with a grant from the Council, he studied the abnormality in quantity and chemical composition of the structures lying behind the eye in a series of thyrotoxic and control subjects on whom post-mortem examinations were made. The exophthalmos was found to be quantitatively related to an increase in bulk of the retrobulbar tissues. This increase was due to an excess of fat which occurred most conspicuously in the eye muscles: parallel investigations of the fat content of the skeletal muscles had to be postponed until after the war. Dr. Pochin also studied the exophthalmos provoked in guinea-pigs by anterior pituitary gland extracts, and related its extent and course to changes in the retrobulbar tissues. These changes were found to differ in character from those causing the exophthalmos in Graves's disease.

With the occurrence of air-raid casualties, studies were made of cases showing symptoms of shock, and the clinical developments in these patients were related to changes in blood pressure, fluid intake and blood volume. The investigations had the purpose of defining the essential features of " shock " and its underlying mechanism. In addition, in relation to the work of Dr. Bywaters and others (p. 52), a group of cases was studied by Dr. Pochin in which symptoms of kidney failure developed some days after a limb had been compressed for a period of hours, usually by débris in air-raid casualties. The presence of myohaemoglobin in the urine of such patients was confirmed, and the amount of its excretion was studied. In an attempt to determine the local vascular changes occurring in the limb after release from compression and ischaemia, Dr. Pochin investigated the results of shutting off the circulation to the rabbit's ear; observations were made on the course of the subsequent oedema, the protein concentration of the oedema fluid, and the conditions in which gangrene developed.

In October, 1940, Sir Thomas Lewis and Dr. Squire undertook the medical teaching of students evacuated to Cardiff. While at Llandough Hospital, they carried out an investigation of the protein content of exudates and transudates. The effects on plasma protein levels of transfusions with blood plasma were studied in selected patients with recurrent ascites and the nephrotic syndrome accompanied by hypoproteinaemia. Rates of transudate formation were correlated with plasma protein levels.

In August, 1941, the teaching of the students was transferred to the U.C.H. Sector Hospital, Stanboroughs, Watford, and Sir Thomas Lewis established a laboratory in connection with this hospital, where the work of the Department of Clinical Research was continued. Studies of asthmatic patients sensitive to foreign proteins had been begun in Llandough Hospital, Cardiff, in collaboration with Dr. D. A. Williams; they were continued by Dr. Squire, with special reference to subjects sensitive to horse dandruff. The protein nature of the excitant in dandruff was confirmed by skin testing, and the reactions of the subjects to horse plasma showed that a different protein, antigenically similar to that in the dandruff, was there involved. The main activity of the horse plasma for these subjects was found to lie in the albumin fraction. These results were confirmed by agglutinin tests using sera from rabbits immunised with horse plasma fractions and dandruff protein. Observations were made of the passive transfer of sensitivity to the skin of normal subjects, by the injection of the serum of those sensitive to horse protein or of

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other patients who showed skin whealing when subjected to heat or cold. Sir Thomas Lewis made detailed studies of the mechanism of whealing in a case of urticaria. The wheals were evoked by various forms of stimulation of cholinergic nerve-endings in the skin, and further light was thrown on antidromic vasodilatation and axon reflexes.

Preliminary work on a histamine antagonist (thymoxy-ethyldiethylamine) confirmed previous publications in showing that guinea-pigs could be protected by this substance against several times the normal lethal dose of histamine injected intravenously.

Sir Thomas Lewis studied the rate of oedema formation in limbs immersed in cold water at various temperatures. Temperatures below 15°C. produced oedema, and the fluid contained about 3 per cent. of protein. These experiments were designed to throw light on the phenomena and treatment of "immersion foot," a condition of extensive damage and swelling of the limbs which was occurring in shipwrecked crews who had been exposed even for short periods to cold water in the North Atlantic and elsewhere. Observations were also made on the results of supercooling the skin, and the different clinical and pathological manifestations of frostbite and related conditions were described, with practical suggestions for their treatment.

Dr. Pochin left the Department in July, 1941, to work in the Council's Physiological Laboratory established at the Armoured Fighting Vehicle Training School, Lulworth, Dorset (see p. 141), and Dr. Squire left in May, 1942, to undertake research in the Royal Army Medical Corps.

An account of the reconstitution of the Department after the period under review will be given in the Council's next Report.

The list of publications below includes some dealing with work done in the Department before the war.

T. Lewis—

Pain. New York (Macmillan), 1942.

Exercises in Human Physiology. London (Macmillan), 1945.

Notes on scleroderma (dermatomyositis). *Brit. J. Derm.*, 1940, **52**, 233.

A note on pulsating manubrial tumour. *Brit. Heart. J.*, 1940, **2**, 260.

Venous pulsation in the orbit. *Clin. Sci.*, 1939–42, **4**, 243.

The adjustment of bloodflow to the affected limb in arteriovenous fistula. *Ibid.*, 1939–42, **4**, 277.

Caleb Hillier Parry, M.D., F.R.S. (1755–1822). A great Welsh physician and scientist. *Proc. Cardiff Med. Soc.*, 1940–41, p. 71.

Observations on some normal and injurious effects of cold upon the skin and underlying tissues. I. Reactions to cold and injury of normal skin. II. Chilblains and allied conditions. III. Frost-bite. *Brit. med. J.*, 1941, **ii**, 795, 837 and 869.

Swelling of the human limbs in response to immersion in cold water. *Clin. Sci.*, 1939–42, **4**, 349.

Trousseau's phenomenon in tetany. *Ibid.*, 1939–42, **4**, 361.

Observations upon the vascular axon reflex in human skin as exhibited by a case of urticaria, with remarks upon the nocifensor nerve hypothesis. *Ibid.*, 1939–42, **4**, 365.

Observations upon a vascular axon reflex. A correction. *Ibid.*, 1944–45, **5**, 5.

Effects of supercooling skin. *Ibid.*, 1944–45, **5**, 9.

Congenital tricuspid stenosis. *Ibid.*, 1944–45, **5**, 261.

Reflections upon reform in medical education. *Lancet*, 1944, **i**, 619, 649, 685.

T. Lewis and J. Stokes—

A curious syndrome, with signs suggesting cervical arterio-venous fistula, and the pulses of neck and arms lost. *Brit. Heart J.*, 1942, **4**, 57.

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R. G. BICKFORD—
The fibre dissociation produced by cooling human nerves. *Clin. Sci.*, 1939–42, **4**, 159.

C. R. HARINGTON, E. E. POCHIN and J. R. SQUIRE—
A simplification of the Evans blue method of blood volume determination. *Clin. Sci.*, 1939–42, **4**, 311.

J. R. HILL and G. W. PICKERING—
Hypertension produced in the rabbit by prolonged renin infusion. *Clin. Sci.*, 1939–42, **4**, 207.

J. H. KELLGREN—
Some painful joint conditions and their relation to osteoarthritis. *Clin. Sci.*, 1939–42, **4**, 193.
Somatic simulating visceral pain. *Ibid.*, 1939–42, **4**, 303.
Sciatica. *Lancet*, 1941, **i**, 561.

E. E. POCHIN—
Oedema following ischaemia in the rabbit's ear. *Clin. Sci.*, 1939–42, **4**, 341.
Exophthalmos in guinea pigs injected with pituitary extracts. *Ibid.*, 1944–45, **5**, 75.

F. F. RUNDLE and E. E. POCHIN—
The orbital tissues in thyrotoxicosis: a quantitative analysis relating to exophthalmos. *Clin. Sci.*, 1944–45, **5**, 51.

J. R. SQUIRE—
An instrument for measuring the quantity of blood and its degree of oxygenation in the web of the hand. *Clin. Sci.*, 1939–42, **4**, 331.

The Clinical Research Unit, Guy's Hospital, London

Staff:—

R. T. Grant, O.B.E., M.D., M.R.C.P., F.R.S. (*Director*).

E. B. Reeve, B.M., M.R.C.P.

Additional staff and attached workers during parts of the war period:—

E. G. L. Bywaters, M.B., M.R.C.P. (*Temporary Director of the Unit for part of its period at Newcastle*).

E. D. Barlow, M.B.

N. A. Neville, B.M., B.Ch.

H. H. Kwiatkowski, M.D., Ph.D.

The Unit's research programme during the war years was concerned mainly with the systematic effects of injury in man. This work was begun during the London air-raids by Dr. Grant and Dr. Reeve. At the outbreak of the war the Unit lost the services of Dr. H. E. Holling, who was called to active service with the R.N.V.R.: his later work, in connection with the Royal Naval Personnel Research Committee, is mentioned elsewhere in this Report.

The initial problem was to learn to recognise and treat the condition known as traumatic or wound " shock ", which was reported to be frequent in air-raid casualties. It was soon apparent that there were wide discrepancies, both from the clinical and the pathological standpoints, between the definitions of " shock ", as recorded in the literature, and the condition actually observed in injured men, and there was also much uncertainty regarding methods of treatment. It was decided that a first requisite towards resolving confusion and bringing order into diagnosis and treatment was to observe and record accurately the details of the state and course in a large number of cases of injury, and to examine their response to therapeutic measures. Only in this way did it seem possible to learn what disorders are produced by injury, how they are caused and how they should be treated.

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The method of study adopted was to follow a case closely at the bedside from the time of the patient's admission to hospital until recovery was assured or until death occurred. In the early stages of the work, few laboratory investigations were made beyond examination of blood samples and of the urine. Later, blood volumes were measured by the dye method in a large number of cases, and more detailed studies were undertaken of the fluid intake and output, and of the metabolic changes associated with injury.

Working in association with the Council's Committee on Traumatic Shock (p. 51), the Unit pursued this study first in London, mainly at Guy's Hospital and at neighbouring hospitals. The cases observed were mostly air-raid casualties, but also included a number of accidental injuries and surgical emergencies. Initially, injuries of all types were observed, excluding only those arising from burning and from prolonged compression (the so-called " crush-syndrome "), which were being intensively studied by other investigators. The first report on 100 cases was submitted to the Committee on Traumatic Shock in July 1941, and the gist of it was published in the *British Medical Journal* in 1941, together with a memorandum on the clinical observations desirable in cases of wound " shock ". From this work it was recognised that, though the phenomena presented by injured patients were various, they could be grouped into several more or less well-defined syndromes; and further, that in producing illness after injury blood loss plays an important part, but it is not the sole factor concerned. On the basis of these observations, it became possible to formulate rules for diagnosis and treatment that proved useful in practice.

The cessation of the large-scale air-raids on London reduced the amount of clinical material accessible for study. Observations were continued, however, on cases of accidental injury, since experience showed, contrary to what had often been stated, that these patients presented the same clinical features and responded to the same forms of treatment as did air-raid casualties. On two occasions stations of Bomber Command were visited, and there a number of instances of injury to aircrew, incurred in bombing raids over enemy territory, were observed. These cases also presented similar features to those already seen in civilians.

While awaiting developments in the war and seeking for new sources of material, other work was continued in temporary laboratory accommodation, the Unit's own laboratories having been destroyed by bombing in September, 1940. Dr. Reeve, dissatisfied with the methods of estimating haemoglobin commonly in use, devised and constructed a photo-electric photometer, and developed methods for estimating haemoglobin which have since served well.

Dr. N. A. Neville, who joined the Unit in March, 1941, and Dr. Reeve carried out observations on the effects of exposure to cold, and on the diurnal variation of haemoglobin. Dr. H. H. Kwiatkowski, who joined the Unit in October 1942, made observations on the histamine content of the blood in injured patients, but, as he was unable to proceed for lack of suitable material, he turned his attention to the effects of antidromic nerve stimulation in animals.

As a result of a survey of hospitals over the whole country in search of sources of clinical material suitable for the intensive studies of the effects of injury, arrangements were made for the Unit to move, at the end of 1942, to the Royal Victoria Infirmary, Newcastle-on-Tyne: this hospital had annually admitted a large number of industrial and road accident cases to its wards. Dr. E. D. Barlow joined the Unit for its stay of just over a year in Newcastle. During Dr. Grant's absence overseas (see below), Dr. E. G. L. Bywaters took charge of the Unit during part of its period of work at Newcastle; his investigations of " crush injuries " and traumatic anuria have been discussed on pp. 51-53, and his publications are listed on p. 352.

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At Newcastle, special, though not exclusive, attention was paid to limb injuries. The reasons for this restriction of the main field of observation were, firstly, that, though cases of injury to head, chest, abdomen or limb all show features in common, they differ significantly in course and treatment, and require separate study; secondly, limb injuries offer the advantage of being common—they comprise about 80 per cent. of all injuries, and are thus of great practical importance; thirdly, in limb injuries no vital structures are involved; and, lastly, in limb injuries it is easier to assess the extent of blood loss, and tissue damage, than in patients with damage to the internal organs. The second report of the Unit on the general effects and treatment of injury in man, based on 120 cases of limb injury, was submitted to the Committee on Traumatic Shock in September, 1943. This work further defined the syndromes recognisable after injury, and indicated that they are brought about by varying combinations of three main factors—blood loss, tissue damage, and nervous disturbances. It also permitted, for this type of case, greater precision to be given to the rules for diagnosis and treatment. The study emphasised, however, the need for further consideration of the two factors of blood loss and tissue damage, so that their effects and relative significance might be determined more precisely. This necessitated access to a larger group of limb injuries, and of severer degree, than was available in civil life. The battlefield alone seemed to offer ample clinical material for the purpose.

In the latter part of 1943, the Council approached the War Office with a view to securing facilities for the continuance of this work in the field in Italy. As a result, a special R.A.M.C. team was formed, including Dr. Grant and Dr. Reeve, Dr. F. Robertson, of the Royal Victoria Infirmary, Newcastle, and, at the instigation of the Anaesthetics Sub-Committee of the Traumatic Shock Committee, Major R. P. Harbord, an anaesthetist already serving with the R.A.M.C. in Italy. Dr. Robertson returned to Newcastle in February, 1945, and was replaced by Major R. J. Rossiter, a biochemist, Three laboratory assistants were provided by the War Office, and the Council supplied the major part of the scientific equipment. The team proceeded to Italy in February, 1944, and worked there, mainly at Casualty Clearing Station level, until the close of hostilities, returning to England in June, 1945. It dealt mainly with limb injuries, studying a series of 110 cases and relating blood loss, and other factors, to clinical state. The work on limb injuries, and particularly the blood volume studies carried out by Dr. Reeve, provided further support for the view that in such injuries by far the most important factor in producing serious illness, at least in the early stages, is blood loss, and that the patient's chances of recovery may be jeopardised by failure to realise the grossness of the haemorrhage and to give enough blood by vein early and quickly enough. Since the number of cases of severe limb injury available for study was insufficient to occupy the full time of the team, the work was extended to include observations on patients with abdominal injuries. Compared with that already gained of limb wounds, the team had had but little experience of abdominal wounds, and consequently a major need was to become acquainted with the details of their state and course, to determine the part played by blood loss, and to analyse the effects due to treatment before, during, and after operation. Though patients with abdominal wounds show features not found in those with limb wounds, haemorrhage is again one of the main factors endangering life in the early stages: it may be said that, before the development of peritonitis, it is the chief factor.

Summarising the conclusions of the work done by the Unit during the war years, the following are the main points that emerge.

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It has become clear that the chief, and dangerous, disorder of patients with limb injuries before, during, and soon after operation is circulatory in origin: that it is seen in those who have bled much before, and sometimes also during, operation; that it is commonly associated with blood volumes in the region of 70 per cent. or less of the predicted normal; the treatment, following immediate control of sources of haemorrhage, is sufficient transfusion before, during and after operation. Sufficient transfusion in some cases has meant the contents of 12 or more pint bottles of blood, plasma or serum. This treatment, which towards the end of the war proved remarkably successful in resuscitating patients even with the most extensive injuries, would earlier have been regarded as gross over-transfusion. No evidence of over-transfusion, however, was encountered, but much of under-transfusion. Death within 48 hours of injury is, in the great majority of cases, due to gross blood loss inadequately treated, transfusion being begun too late, given too slowly, or in insufficient quantity. Death occurring at a later stage is due mainly to complications of injury, such as wound infection, fat embolism or renal failure. The renal failure may be the result of inadequate transfusion in the early stages, though other factors may be concerned.

It follows that in dealing with limb injuries, which form the great majority of all injuries however caused, the recognition, assessment and treatment of blood loss in the initial stages are of prime importance. Assessment of blood loss is most accurately accomplished by measuring blood volume. But the methods at present available are neither sufficiently simple nor rapid enough for routine use at the bedside; experience shows that, though blood volume estimations are of great assistance, the great majority of cases can be treated successfully without their aid.

In the first place it is clear that, in general, the larger the wound the greater the amount of bleeding, and it has been found that a rough estimate of the volume of tissue damaged (using a man's hand as the unit of volume) provides a good and practicable index of blood loss. Secondly, analysis of the clinical findings in relation to measured blood volumes has shown that, in most instances, as blood loss increases and blood volume falls, such signs as low blood pressure, rapid pulse, facial pallor and coldness of the extremities become evident. In fact, it was the team's experience that *all* patients with limb injury displaying this syndrome in its entirety, irrespective of the degree of injury, had lost much blood (having blood volumes below 70 per cent. of normal) and required transfusion urgently. On the other hand, the presence of a normal blood pressure and pulse rate, and a well coloured face, together indicate that blood loss has been small (blood volume over 80 per cent. of normal). While there is generally little difficulty in recognising those who have lost either much or little blood, there is considerable difficulty with those who have lost intermediate amounts. With blood volumes between 70 and 80 per cent. of normal, blood pressure is normal, but facial pallor and a fast pulse, though usual, are by no means constant. Moreover, factors other than haemorrhage, such as environmental temperature, tissue damage, emotion, age or the pharmacological effects of earlier transfusions, may influence the clinical picture and complicate the assessment of blood loss.

During operation, which may justly be regarded as a second injury, the circulatory changes are very similar to those which occur as a result of the primary injury. Here again, there are further modifying factors. Thus the anaesthetic and the method of administering it, the pre-operative medication, transfusion, the warming or cooling of the patient on the operating table, may each modify the state of the circulation. Nevertheless, the most important single factor in the genesis of the circulatory changes during operation is blood loss and its treatment. Provided that previous blood loss has been

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adequately treated and that no great bleeding occurs during operation, patients can withstand long and severe operations without developing circulatory failure. This holds true irrespective of the degree of tissue damage, and whether or not the patient initially showed circulatory collapse. In the early stages after operation, the level of the blood volume is of chief importance in determining the state of the patient's circulation, and, in gauging this, the record of the blood pressure is the simplest guide.

In addition to the studies outlined above, attention was paid to certain other clinical, pathological and biochemical sequels to trauma—for example, the continued loss of red cells from the circulation after operation despite the arrest of haemorrhage and the control of infection; the tissue wasting which is reflected in a negative protein balance; the loss of chlorides which is prone to occur not only in abdominal injuries as a result of continuous gastric suction but also in very large limb injuries; and disturbances of renal function. Observations on these aspects of the response to injury were, however, curtailed by the end of the war.

R. T. Grant—
Observations on air raid casualties. *Guy's Hosp. Gaz.*, 1941, **55**, 90.
Contribution to Discussion on "Methods of resuscitation in shock." *Proc. R. Soc. Med.*, 1942, **35**, 445.

R. T. Grant and E. B. Reeve—
Clinical observations on air-raid casualties. *Brit. med. J.*, 1941, **ii**, 293 and 329.

H. Kwiatowski—
Histamine in nervous tissue. *J. Physiol.*, 1943, **102**, 32.

E. B. Reeve—
Observations on the photo-electric estimation of total haemoglobin. *J. Path. Bact.*, 1944, **56**, 95.

E. B. Reeve and N. A. Neville—
A simple standard procedure for obtaining blood having a haemoglobin content identical with arterial blood. *Clin. Sci.*, 1945, **5**, 1.

The Neurological Research Unit, National Hospital, Queen Square, London

Staff:—
E. Arnold Carmichael, C.B.E., M.B., F.R.C.P. (*Director*).

Attached civilian workers during the whole or part of the period covered:—
C. S. Hallpike, M.B., F.R.C.P., F.R.C.S. (*see* p. 264).
Miss Julia Bell, F.R.C.P.
B. McArdle, M.D., M.R.C.P.
J. W. Magladery, M.D. (*Captain, R.C.A.M.C., from January, 1942*).
A. M. Joekes, B.M. (*joined R.A.F. Medical Service, 1942*).
W. S. S. Ladell, M.R.C.S., L.R.C.P.
J. S. Weiner, M.Sc.
J. C. Waterlow, M.D.
J. C. D. Hutchinson, M.A.
G. D. Dawson, M.Sc., M.B.
B. S. Platt, C.M.G., M.Sc., Ph.D., M.B.
R. A. Webb, D. Phil. } (*see also* p. 284).

(*The names of Service medical officers who worked in the Unit during the war are given in the text.*)

At the outbreak of war, the research programme of the Unit was at first much curtailed. In September, 1939, the Hospital was temporarily evacuated, and the laboratories were taken over by the Holborn Borough Council as a

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First Aid Post. A few weeks later, a limited number of beds was re-opened at the Hospital and some laboratory space became available; this permitted the resumption of research work. As it proved impossible, owing to lack of suitable laboratory facilities, to continue previous studies of the sympathetic nervous system, efforts were directed to the solution of practical problems arising directly from the war.

Many of the investigations described below were carried out for the Flying Personnel Research Committee of the Air Ministry, and for the Military Personnel Research Committee and the Royal Naval Personnel Research Committee appointed by the Council at the request of the War Office and the Admiralty respectively; a general account of the work of these committees and their principal sub-committees has been given on pp. 131-152. Dr. E. A. Carmichael, the Director of the Unit, was Secretary of the Military Personnel Research Committee; he also served on the Flying Personnel Research Committee and on varous sub-committees dealing with personnel problems. In the following summary of studies made by workers in the Unit and their collaborators, it has not been practicable to separate the inquiries made for the respective Services and Personnel Research Committees, as these were very closely interlinked, the solutions provided by research to the problems of one Service often being equally applicable to those of another.

In the list of references given at the end of the Unit's report, only papers published before the end of September, 1945, are included; the results of many more studies were submitted in confidential reports to the Personnel Research Committees and the Service Departments during the war, though some of them have since been published.

Before their own Units were established (pp. 264 and 284), Dr. Hallpike and Dr. Platt, of the Council's staff, worked in this Unit during part of the war period. Dr. Julia Bell, who retired from the Council's staff in January, 1944, also worked here during the war.

Mr. Weiner, whose research with the Unit is described below, was appointed University Reader in Physical Anthropology at Oxford in January, 1945, but he was seconded thereafter to the Council's temporary service on a part-time basis, and continued working with the Unit throughout the remainder of the period covered by this Report.

Personnel Research

High altitude flying.—Various factors connected with high altitude flying were studied by Dr. Carmichael and Dr. McArdle early in the war. With the late Professor B. A. McSwiney, of St. Thomas's Hospital, the influence of cold on the circulation, and the effect, under such conditions, of breathing high concentrations of oxygen, were examined; these and other investigations undertaken for the Flying Personnel Research Committee (p. 132) led subsequently to the design of suitable flying clothing for aircrew likely to be exposed to extreme cold. For the same Committee, Dr. Carmichael took part in work on the painful cramps (" bends ") which occur after exposure to rarified atmospheres, and Dr. McArdle collaborated with Dr. Brian Matthews, of the Royal Aircraft Establishment, Farnborough, in studying certain metabolic disturbances occurring under conditions simulating those of flight at high altitudes.

Water rations for shipwrecked personnel.—While working in this Unit, Dr. Platt, as Secretary of the Committee on the Care of Shipwrecked Personnel (p. 419), supervised the studies relating to the water requirements of the shipwrecked, for which a small group of volunteers headed by Dr. Ladell served as the subjects; this work has been mentioned on p. 100.

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Motion-sickness (*sea-sickness and air-sickness*).—Dr. McArdle and Dr. (later Captain) Magladery co-operated with Dr. G. L. Brown of the National Institute (p. 203) in the design of a swing for producing motion-sickness in man, and in investigating the disturbances of the alimentary system associated with the onset of motion-sickness. Dr. Hallpike studied the labyrinthine responses in a series of Service personnel subjected to violent movement and loud noises; he also arranged for volunteers with bilateral absence of function of the labyrinths, to be tested on the swing—it was shown that such subjects were insusceptible to motion-sickness (p. 139). In extension of these and other laboratory studies, Dr. McArdle, with Surg. Lt.-Cdr. H. E. Holling, R.N.V.R., and Captain W. R. Trotter, R.A.M.C., carried out a series of trials at sea of various drugs recommended for motion-sickness; their report, which has been published, showed that hyoscine, in small doses, was the best of the remedies tested; it has since been widely used for the purpose in the Fighting Services. The possible use of selection measures for air-borne troops and R.A.F. bomber crews, in order to determine in advance their liability to motion-sickness, was examined by Dr. Magladery and F./Lt. A. M. Joekes, R.A.F.V.R. In addition, facilities to use the swing for study of disturbances of eye-muscle balance in motion-sickness were given to Brigadier Sir Stewart Duke-Elder and Air Commodore P. C. Livingston.

Armour.—Dr. Carmichael, with the late Dr. K. J. W. Craik (pp. 133-4), reported, after various physiological and physical tests, upon the relative merits and defects of vizors designed to protect the eyes against injury by battle missiles. Dr. Hallpike, while working in the Unit, undertook a careful analysis of chest wounds; the information obtained from this, and from *ad hoc* experiments, enabled him to recommend a design of body armour for the Army (p. 136).

Climatic and environmental studies.—In 1942 Dr. Carmichael, Mr. Weiner, Dr. McArdle and other workers in the Unit began an extensive series of investigations into methods of improving the comfort and fighting efficiency of men exposed to high temperatures. On behalf of the Armoured Fighting Vehicles Sub-Committee of the Military Personnel Research Committee, studies were undertaken which led to the development of ventilated clothing for the use of tank crews (pp. 142 and 260). Valuable experience had already been gained in the equipment and running of a small "hot room" at the London School of Hygiene, and for the extension of the researches on climatic problems another small hot room was erected at the National Hospital.

At about this time, the Admiralty were concerned lest the physical conditions in warships were such as to impair the fighting efficiency of their crews, from inability to withstand the very hot humid environment in ships ready for action in the tropics. Accordingly, after consultation with the Council and with the Board and Medical Committee of the National Hospital, the Admiralty arranged in 1943 for the construction of two larger experimental hot rooms at the Hospital, in which dry and wet bulb temperature, and air movement, could be accurately controlled. The Admiralty also posted Naval Officers to the Unit, and called for volunteers to act as subjects in this experimental work. Observers sent out by the Royal Naval Personnel Research Committee to the Fleet in the Far East had obtained records of temperature, and air movement, in various compartments of different classes of warship (p. 150). With this information available, it was possible to create similar conditions in the experimental rooms. Officers from the operational staff of the Royal Navy then advised as to the amount of work required of the volunteers; this was defined in terms of the number of rounds of 6-inch ammunition, or of 12- to 15-inch ammunition, to be fired in a given

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time. For the purpose of the experiments, the breach of a 6-inch gun was erected in one of the Unit's laboratories, measurements being made of the amount of work performed by each member of its crew. Dummy cordite charges, with racks, were provided for simulating magazine conditions, and further work studies were undertaken. The results were checked against those obtained at gunnery training establishments and in ships firing at sea.

With the erection of the two new hot rooms by the Admiralty, work on climatic physiology was intensified. Dr. McArdle, Dr. Ladell and Mr. Weiner devoted their whole time to these studies and had assisting them Surg. Lt.-Cdr. Holling, Surg. Lt.-Cdr. R. C. S. Benson, R.N.V.R., Surg. Lt.-Cdr. T. Colver, R.N.V.R., Surg. Lt.-Cdr. J. W. Scott (of the Royal Canadian Navy), Surg. Lt. W. F. Dunham, R.N.V.R., and Surg. Lt. M. L. Thomson, R.N.V.R.

Before being submitted to the full range of investigations in the hot rooms, all the subjects had to be acclimatised to work in a " tropical " environment. For this a routine was established, necessitating daily work for three weeks in very hot humid conditions. Arrangements were made to compare the reactions of the acclimatised subjects at the National Hospital with those of naturally acclimatised Naval ratings doing similar work in the tropics. It was found that the system of acclimatisation adopted in the laboratories resulted in the men being, if anything, better able to withstand hot and humid conditions than were those actually stationed in the Far East. The acclimatised men were then put to work in the hot room, as if in action as members of a crew of either a 6-inch gun or a 15-inch gun. It was found that during a work period of four hours each man might lose as much as 14 to 18 pints of sweat and, with this, 21 to 27 grams of salt, the daily intake of salt in the food being, for normal people, in the region of 15 grams. Further the body temperatures of the men rose not infrequently to 103° to 105° F. Such conditions were obviously a tremendous strain on the men, and there were occasions when " heat-collapse " occurred, requiring urgent removal from the hot room, and resuscitation. In some men " heat-cramps " occurred; these caused severe pain and temporary incapacitation. The fortitude of the volunteers who daily submitted themselves to such stress and strain is worthy of note. During the experiments in the hot rooms, it became evident that the performance of work deteriorated when men were first exposed to high temperatures. Mr. Weiner and Mr. Hutchinson made a special study of this, and found that dexterity fell on single exposures to heat, even though the subjects had been acclimatised. When, however, the subjects persevered in working in the hot room over a number of days, dexterity improved to as high a level as that noted in a cool environment. It thus appears that, besides being acclimatised, a man requires to be practised in working in a hot climate.

Dr. McArdle had previously used the hot rooms to determine an efficient method of utilising man-power for pedal-operated generators under tropical conditions; a study was made of the limiting environmental conditions for efficient work. The main variables in this series of experiments were dry bulb temperature, wet bulb temperature, level of air movement, and the nature and amount of the work and clothing.

In relation to the various studies mentioned above, a method of measuring environmental warmth was required which took adequate account of all the physical factors involved. The " effective temperature " scale had been used to a large extent in similar researches in industry; but, when the scale was devised by American workers before the war, the rigorous conditions later encountered in the Navy in tropical waters had not been envisaged. It was therefore necessary to investigate the accuracy and suitability of the scale for such exceptionally severe environments, and to assess

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the parts played by dry bulb temperature, humidity, and different levels of air movement, on the ability of acclimatised men to perform different grades of work. Many experiments have been directed towards determining these points, and the results have indicated that environmental conditions previously reported as likely to lead to early death have in fact been compatible with survival. They have further shown that, at certain temperature levels on the scale, the loading by the wet bulb reading is too low and requires revision, and that insufficient attention had been paid to the effects of radiation in constructing the scale. Study of the effect of various levels of air movement at different effective temperatures has shown that, in general, an increase of air movement improves efficiency, but too great an increase may reduce it. Dr. J. O. Irwin, of the Council's Statistical staff, assisted in planning this lengthy and complicated investigation, involving hundreds of individual tests. The data which have been collected, and which are now being prepared for publication, should provide a valuable yardstick for assessing the work performance possible under varied environmental conditions. In the work on methods of measuring environmental warmth, Dr. T. Bedford, of the Council's staff at the London School of Hygiene, co-operated with members of the Unit.

Under-water studies.—Owing to high sea-temperatures, hot and humid atmospheric conditions, the presence of coral reefs, and the inhabitation of tropical seas by stinging and man-eating fish, the work of divers in tropical waters has risks not met with in more temperate regions. It was therefore necessary to determine the capacity of men to undertake diving or under-water swimming with equipment giving protection against these dangers. Mr. Hutchinson and Mr. Weiner visited naval establishments connected with this type of work, and made measurements of the energy consumption involved in the various under-water operations performed. Returning to the Unit's laboratories, they produced similar working conditions in a water tank. They were thereby able to study the effect of wearing various types of diving and under-water swimming gear on the efficiency of acclimatised subjects. From the results of these experiments it was clear that the available equipment required modification, and special clothing was designed, made from a carefully selected drill. Before the end of the war against Japan Mr. Hutchinson went to the Far East, to advise on the physiological aspects of this type of warfare.

Ventilated clothing and other equipment for tropical climates.—In 1942 Dr. McArdle and Dr. Waterlow, working in the hot room, began a study of measures designed to improve the environmental conditions inside armoured fighting vehicles; later, Mr. Hutchinson joined them in this study. The work culminated in the development of a " ventilated suit " for the use of tank crews (p. 142). The design of this suit was based on pioneer studies by Dr. McArdle and Mr. Weiner, in which they examined the possibility of introducing limited quantities of air beneath the clothing as a means of increasing efficiency in hot environments. Dr. McArdle and Dr. J. A. B. Gray, with personnel of the Royal Armoured Corps and of the Directorate of Special Weapons and Vehicles, carried out a series of trials of the ventilated suit in a tank. The tank was placed in a specially equipped laboratory at the National Physical Laboratory, Teddington, in which jungle conditions could be simulated while still allowing the tank engine to be run and the guns to be fired. The value and practicability of the ventilated suit were demonstrated, and comparisons were made between the gains in efficiency due to the suit and those due to improved tank ventilation. As a result of this work, the Directors, respectively, of the Royal Armoured Corps and of Tank Design

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placed an order for this equipment. It was made under the supervision of the members of the Unit and was then shipped to the Far East, where Mr. Hutchinson arranged field trials confirming its efficiency. In view of the implications of this work for those engaged in mining operations in hot environments, the Government of the Union of South Africa requested the Council to provide them (for their Department of Mines) with a report of the work: this was prepared by Dr. McArdle and Mr. Weiner.

Dr. McArdle, Dr. Ladell and Mr. Weiner also examined the suitability of various mosquito-proof fabrics for use as uniforms in the tropics. After a series of comparative tests had been completed, recommendations were submitted to the Services concerned. As a result of these studies, the Council were asked by the Director of Special Weapons and Vehicles, and the Quartermaster General, to permit members of their staff to assist in the design and testing of numerous articles of equipment for the Army in the Far East. In this way much useless manufacturing effort and expense were avoided.

Water balance in hot environments.—Mr. Weiner elaborated a new technique for the collection of sweat; among other studies made possible by this technique has been the determination of the regional distribution of sweating due to heat. During prolonged exposure to heat Dr. Ladell found that both the secretion of sweat, and its content of salt, were diminished; he postulated that fatigue of the sweat glands takes place. Dr. McArdle and Mr. Weiner noted that, on repeated exposure to hot environments, the sweating rate increased and sweating started earlier, and at a lower body temperature, than previously. Dr. Ladell reported on the changes that occur in the chloride concentration of sweat with acclimatisation, and studied certain factors, such as rapid, or slow, acclimatisation to heat, varied fluid and salt intakes, and dehydration, which affect the amount and composition of the sweat. These investigations entailed measurements of sweating rate, estimation of chloride concentration in the sweat, of urine output, of urinary chloride concentration, and of blood chloride concentration. Surg. Lt. Dunham studied sweating rates under various environmental conditions, particularly in relation to the temperature of the skin surface. With Professor A. A. Miles (pp. 31 and 266), he also made preliminary observations on the bacteriology of the skin and on the mode of spread of skin pathogens in the hot room, in view of the potential bearing of these questions on the problem of skin affections (including prickly heat) in the tropics. Surg. Lt.-Cdr. Scott made a study of the effect of the drug, hyoscine, on the sweat rate, cardiac rate, and the general ability of men to work in hot environments. This study arose from the prevalent use of hyoscine as a remedy for motion sickness (p. 258). It was found that hyoscine reduced the men's capacity to sweat, with a resultant rise in body temperature and a decrease in efficiency at work, but the changes were of comparatively short duration and, in ordinary circumstances, of relatively little importance.

Dr. Ladell and Mr. Weiner studied the factors responsible for the small output of urine observed in hot climates, and attempts were made to decide whether it is due to changes in the blood supply to the kidneys, or in glomerular and filtration function, or to alterations in the hormonal control of the kidneys. This led to the study, in man, of methods of assaying the posterior pituitary antidiuretic hormone as excreted in the urine. Mr. Weiner completed a study of the survival of animals at high temperatures, with special reference to the part played by the adrenal and related hormones, and Dr. Ladell reported on the effects of desoxycorticosterone acetate on the chloride concentration of the sweat.

Heat collapse and heat cramps.—In 1943, at the request of the War Office, Dr. Ladell and Dr. Waterlow were sent to Iraq to study heat casualties, and to advise on methods for their prevention and treatment (p. 101). The clinical

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features of the various types of heat casualty were defined, and biochemical studies were made on both casualties and healthy men. These studies suggested that individual differences in the rate of sweating, and in the salt content of the sweat, might be decisive in determining whether a man was likely to succumb to heat exhaustion. In relation to this field work, Mr. Hutchinson and Mr. Weiner made a study of the underlying causes of heat collapse, in the hot rooms at the National Hospital.

With Dr. Ladell and Dr. Carmichael, Dr. Dawson carried out an analysis of the mechanism of " heat cramps ". Dr. Ladell was the volunteer subject for these experiments: following strenuous physical work in the hot room, during which he replaced water lost in the sweat but not the chloride, he suffered from severe cramps in the muscles. It was established that, although the disturbance arises primarily in muscle, it is dependent on the integrity of the spinal reflex arc.

The designing of much new equipment was necessary for this work and for other investigations which arose from it. For instance, a new type of time base and stimulator was built for producing and recording the reactions of muscles to two successive stimulations of a peripheral nerve. Similarly a two-channel, ink-writing electrocardiograph was built for use in connection with some of the hot room work.

The work in the hot rooms continued until the beginning of 1946, when they were finally closed.

Protective clothing.—The risk to naval personnel from burns due to the flash of high explosives, or due to fires, has been met by the design of light-weight anti-flash clothing. In studies bearing on this question Dr. R. B. Bourdillon and Dr. O. M. Lidwell, of the Council's staff at the National Institute (pp. 203 and 209), co-operated with Mr. Weiner and Mr. Hutchinson; much help was given also by the British Cotton Industry Research Association, and the Wool Industries Research Association.

The need for wearing flotation gear by naval personnel raised further problems, as gear suitable for use in the Atlantic, North Sea and Channel would throw too great a heat load on men in the tropics. As a result of studies in which Mr. Hutchinson, Mr. Weiner and Surg. Lt.-Cdr. Holling took a prominent part, flotation gear was eventually designed which was suitable for use in the Far East.

The protection of airmen against the cold of high altitudes and the effect of " G " necessitates the wearing of cumbrous clothing: this lays a heavy heat load on crews standing by for action. The need for the development of such protective clothing, suitable for use in the tropics, was apparent to the physiological team working at Farnborough under Dr. Matthews, and the co-operation of the Unit was sought in the design and testing of this equipment.

Neurological Studies

Sulphonamides in wounds of the brain (p. 48).—With Colonel W. V. Cone and Major E. H. Botterell, of the Royal Canadian Army Medical Corps, experimental studies were made of the effect of inserting certain members of the sulphonamide group of drugs, in powder form, into wounds of the brain. It was shown that sulphanilamide was readily absorbed; sulphapyridine to a lesser extent. No evidence was obtained that the healing process was delayed by the presence of these drugs in moderate amount.

Vitamin therapy in neurological disorders.—Dr. McArdle and Dr. G. Fitzgerald, then a house physician at the Hospital, investigated the effects of vitamin E and vitamin B_6 on patients with muscular dystrophies and motor neurone disease. It was established that in these conditions α-tocopherol (vitamin E) was of no benefit.

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Hereditary factors in neurological disorders.—Dr. Julia Bell completed in the Unit an investigation of the consanguinity rate in the hospital population of England and Wales, and began a series of studies on the inheritance of the muscular dystrophies: material was also collected for an investigation into familial periodic paralysis.

Pethidine.—As mentioned on p. 42, Dr. Fitzgerald and Dr. McArdle carried out clinical trials, in the Unit, of the value of the synthetic drug, pethidine, in alleviating pain in patients with neurological disorders.

Myasthenia gravis.—In association with Air Vice-Marshal G. L. Keynes, Dr. J. Carson and others, Dr. Carmichael began in 1942 an investigation into the value of thymectomy in myasthenia gravis. Many patients have had the operation, but it is as yet too early to make a definite pronouncement as to the place of surgery in this disease. Work on myasthenia is being continued in the Unit.

Electro-encephalography.—Dr. Dawson, in collaboration with Dr. W. Grey Walter, completed a report on the scope and limitations of visual and automatic analysis of the electro-encephalogram. A new design for an electro-encephalographic recorder was evolved: since the end of the period covered by this Report it has been used in studies of epilepsy.

Other studies

For convenience, the nutritional studies made by Dr. Platt and Dr. Webb while working in this Unit, are discussed with Dr. Platt's other nutritional researches, on pp. 284-5.

In addition to his work with the Unit, Dr. McArdle took part in a field survey of problems of health and efficiency in a wartime factory (see p. 325).

J. Bell—

On the age of onset and age at death in hereditary muscular dystrophy with some observations bearing on the question of antedating. *Ann. Eugen.*, 1942, **11**, 272.

J. Bell and E. A. Carmichael—

On hereditary ataxia and spastic paraplegia. *Treas. Human Inheritance*, 1939, **4**, 141.

E. H. Botterell, E. A. Carmichael and W. V. Cone—

Sulphanilamide and sulphapyridine in experimental cerebral wounds. *J. Neurol. Psychiat.*, 1941, **4**, 163.

E. A. Carmichael, W. M. Honeyman, L. C. Kolb and W. K. Stewart—

A physiological study of the skin resistance response in man. *J. Physiol.*, 1941, **99**, 329.

Peripheral conduction rate in the sympathetic nervous system of man. *Ibid.*, 1941, **99**, 338.

G. D. Dawson—

The relation between the electroencephalogram and muscle action potentials in certain convulsive states. *J. Neurol. Neurosurg. Psychiat.*, 1946, **9**, 5.

G. D. Dawson and W. G. Walter—

The scope and limitations of visual and automatic analysis of the electroencephalogram. *J. Neurol. Neurosurg. Psychiat.*, 1944, **7**, 119.

Recommendations for the design and performance of electroencephalographic apparatus. *Ibid.*, 1945, **8**, 61.

G. Fitzgerald and B. McArdle—

Vitamins E and B_6 in the treatment of muscular dystrophy and motor neurone disease. *Brain*, 1941, **64**, 19.

Effect of pethidine on pain in neurological cases. *Lancet*, 1943, **i**, 296.

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H. E. HOLLING, B. MCARDLE and W. R. TROTTER—
Prevention of seasickness by drugs. *Lancet*, 1944, **i**, 127.

W. S. S. LADELL—
Effects of drinking small quantities of sea water. *Lancet*, 1943, **ii**, 441.
Thermal sweating. *Brit. med. Bull.*, 1945, **3**, 175.
The effect of desoxycorticosterone acetate on the chloride content of the sweat. *J. Physiol.*, 1945, **104**, 13P.

W. S. S. LADELL, J. C. WATERLOW and M. F. HUDSON—
Desert climate: physiological and clinical observations. *Lancet*, 1944, **ii**, 491 and 527.

W. S. S. LADELL (introduced by B. S. PLATT)—
Changes in the chloride concentration of sweat with acclimatization. *Biochem. J.*, 1945, **39**, xlviiP.

J. P. MARTIN and J. BELL—
A pedigree of mental defect showing sex-linkage. *J. Neurol. Psychiat.*, 1943, **6**, 154.

B. MCARDLE—
The effect of breathing pure oxygen on the nitrogen dissolved in the cerebro-spinal fluid. *J. Physiol.* 1945, **103**, 35P.

J. S. WEINER—
The regional distribution of sweating. *J. Physiol.*, 1945, **104**, 32.

J. S. WEINER and J. C. D. HUTCHINSON—
Hot humid environment: its effect on the performance of a motor co-ordination test. *Brit. J. industr. Med.*, 1945, **2**, 154.

The Otological Research Unit, National Hospital, Queen Square, London

Staff and attached workers:—

C. S. Hallpike, M.B., F.R.C.P., F.R.C.S. (*Director*).

M. E. S. Harrison, M.D., M.R.C.P.E., F.R.C.S.E.

Miss Margaret R. Dix, M.B., F.R.C.S.

J. D. Hood, B.Sc.

This Unit was established, by arrangement between the Council and the Medical Committee and Board of Management of the National Hospital, in 1944. During the earlier years of the war Dr. Hallpike worked in the Neurological Research Unit directed by Dr. E. A. Carmichael, as already mentioned on p. 257. Some of his *ad hoc* studies for the Personnel Research Committees have been noticed elsewhere in this Report; they included an analysis of the aural causes of rejection of aircrew candidates, co-operation in the work on motion sickness (pp. 133, 139 and 258), work on the design of body armour (pp. 136 and 258), and investigations of the nature and prevention of the aural effects of muzzle blast and of gun and engine noise.

The principal items of the Unit's research programme have been clinical studies of vertigo, clinical and electro-acoustic studies of deafness and the use of hearing aids, and studies of the pathology of the inner ear.

In the work on vertigo, Dr. Hallpike has had the co-operation of Mr. Harrison and Miss Dix. It has included observations on Ménière's disease, and detailed analyses of vestibular and cochlear function in certain organic diseases of the central nervous system and psychosomatic diseases. The vestibular reactions in patients with neurosis and psychoneurosis have been examined by Mr. Harrison at Sutton Emergency Hospital, by courtesy of the Superintendent.

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For the work on deafness and hearing aids, special accommodation, converted to include sound-proofed rooms, was provided at the National Hospital, where a Deafness Clinic was temporarily established in the summer of 1945. Here patients with all types of deafness, except that accompanied by active otitis media with ear discharge, were examined clinically and instrumentally as to their suitability for medical or surgical treatment, and as to their requirements of hearing aids where these might be of benefit. The studies had an important bearing on the work on the design of new types of portable hearing aids which was undertaken by the Council's Committee on Electro-acoustics (p. 426) with the co-operation of engineers at the Post Office Research Station. A report by this Committee, on hearing aids and audiometers, has since been published in the Council's series. It describes the development of prototype models of small, electrically-operated aids, which have been found suitable for most types of deafness, and should be relatively cheap to produce and maintain. These aids are now being manufactured under arrangements made by the Ministry of Supply on behalf of the Ministry of Health, and it is intended that they shall be prescribed to patients through special clinics set up by the Ministry of Health as part of the new National Health Service. In view of the very large number of inquiries which have reached the Council's office since the first announcements about these aids were made, it should be emphasised here that they will *not* be issued by the Council.

Dr. Hallpike's pathological studies have been concerned with the histology of the temporal bone in various abnormal conditions. An extensive series of observations has been made on the embryology of the inner ear in the inherited deafness of white cats. The findings, which should assist in elucidating the mechanism of certain types of human deafness, are being prepared for publication. Through the help of Mr. T. E. Cawthorne it has been possible to obtain material for pathological examination from another case of Ménière's disease. The changes found in the temporal bones reproduced very faithfully those described in a number of previous examples of this condition. Technical research on the manufacture and sharpening of large microtome knives, suitable for use in studies of the histology of the skull bones, has been carried out in co-operation with the staff of the Metrology Division of the National Physical Laboratory.

COMMITTEE ON ELECTRO-ACOUSTICS—
Hearing aids and audiometers. *Spec. Rep. Ser. Med. Res. Coun., Lond.*, No. 261, 1947.

P. ALDRED, C. S. HALLPIKE and A. LEDOUX—
Observations on the osmotic pressure of the endolymph. *J. Ph s ol.*, 1940, **98**, 446.

T. E. CAWTHORNE, G. FITZGERALD and C. S. HALLPIKE—
Studies in human vestibular function. II. Observations on the directional preponderance of caloric nystagmus ("Nystagmusbereitschaft") resulting from unilateral labryinthectomy. *Brain*, 1942, **65**, 138. III. Observations on the clinical features of Ménière's disease, with especial reference to the results of the caloric tests. *Ibid.*, 1942, **65**, 161.

T. E. CAWTHORNE and C. S. HALLPIKE—
Some recent work on the investigation and treatment of "Ménière's disease" *Proc. R. Soc. Med.*, 1943, **36**, 533.

G. FITZGERALD and C. S. HALLPIKE—
Studies in human vestibular function. I. Observations on the directional preponderance ("Nystagmusbereitschaft") of caloric nystagmus resulting from cerebral lesions. *Brain*, 1942, **65**, 115.

H. GRÜNEBERG, C. S. HALLPIKE and A. LEDOUX—
Observations on the structure, development and electrical reactions of the internal ear of the shaker-I mouse. *Proc. R. Soc.*, B, 1940, **129**, 154.

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C. S. HALLPIKE—
Notes on the progress and future rôle of research in otology. *Brit. med. Bull.*, 1944, **2**, 119.

C. S. HALLPIKE and P. SCOTT—
Observations on the function of the round window. *J. Physiol.*, 1940, **99**, 76.

The Wound Infection Research Unit (Unit for Research on Industrial Injuries), Birmingham Accident Hospital and Rehabilitation Centre

Staff:—

Professor A. A. Miles, F.R.C.P. (*Director*).

R. E. O. Williams, M.D. (*Resident research pathologist; Acting Director*, 1945).

Miss B. Clayton-Cooper, B.Sc.

Miss Brenda Moss, B.Sc.

The experience of infection in wounds of military casualties in Great Britain in the early years of the war made it clear that our knowledge of prophylaxis and treatment of wound infections was in many respects insufficient. Accordingly, in 1942, after discussions between representatives of the Council and Mr. William Gissane, the Clinical Director of the Birmingham Accident Hospital and Rehabilitation Centre, arrangements were made by the Council to establish there a Unit for research on wound infection, in relation particularly to industrial injuries. Professor A. A. Miles (p. 31) was made Director of the Unit, by permission of the Ministry of Health and the authorities of University College Hospital Medical School, London, and Dr. R. E. O. Williams was seconded from the Emergency Medical Service as resident research pathologist. Miss B. Clayton-Cooper was research assistant for two years, and was succeeded by Miss Brenda Moss. This Unit was a separate organisation from that for research on burns, directed by Dr. Leonard Colebrook, of the Council's staff, which was later established at the same hospital (p. 270), but there was close co-operation between the two Units on matters of common interest.

The Birmingham Accident Hospital, and the surgeries in the Birmingham factories with which it was closely associated, were peculiarly favourable for the study of wound infection. The number of injured patients received there was large and, with the collaboration of factory Medical Officers, many of the industrial wounds could be observed continuously, almost from the moment of infliction to the time of complete healing. Moreover, wounds of certain types being very common, there was material for making extensive comparative tests of various methods of prophylaxis and treatment, and thereby evaluating precisely methods whose rationale had hitherto been based on inadequately controlled trials.

The work of the Unit during the four years 1942-1945 falls under four heads:—The epidemiology of wound infection; the effect of infection on the wound; prevention and treatment of wound infection; and miscellaneous laboratory investigations on cognate subjects.

The main programme of the Unit was completed by the end of the period covered by this Report; Professor Miles had already been appointed to the Council's staff at the National Institute for Medical Research, to take charge of the work on biological standards, in succession to Sir Percival Hartley, and Dr. Williams, who for a time served as Acting-Director of the Unit, later joined the Public Health Laboratory Service (p. 166). It was

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agreed, however, between the Council and the authorities of the Birmingham Accident Hospital, that the facilities provided for the Wound Infection Unit could effectively, and with only minor modifications, be adapted to the formation of a new Research Unit in Industrial Medicine, which should continue the investigations of wound infection but should also give special attention to the problem of skin disease due to industrial hazards. A Unit with these terms of reference was subsequently established at the Hospital, as mentioned on p. 154, and Dr. J. R. Squire was appointed its Director.

The four chief groups of studies made in the Wound Infection Unit from 1942 till 1945 are considered below in greater detail.

Epidemiology of Wound Infection

It was clear at the outset that neither the available time and staff, nor the *a priori* knowledge of the subject, would permit an investigation of the epidemiology of wound infection, except incidentally, by studying the reaction of patients with infected and uninfected wounds. It appeared to be more immediately profitable to determine (*a*) what the infecting microbes were, (*b*) at what time in its history they entered the wound, and (*c*) where they came from.

From a study of over 2,500 wounds, mainly of the hand, the following findings emerged. Wounds are most commonly infected with *Staphylococcus aureus*, and less commonly, though often rather more severely, by *Streptococcus pyogenes;* in wounds of the hand, infection by microbes derived from the gut is relatively uncommon. *Staph. aureus* commonly enters the wound at the moment of injury, but may also invade it during the rest of its course; *Str. pyogenes* tends to be added late in the history of the wound. Infection by these two micro-organisms may be derived from other wounds—particularly in surgeries, hospital outpatient departments and wards—and also from healthy human carriers, especially the patient himself. *Str. pyogenes* is carried, relatively infrequently, in the throat. *Staph. aureus,* on the other hand, is carried more or less permanently in the nasal cavities of 70-80 per cent. of normal adults, and from there may infect a wound directly, or indirectly, by reason of its frequent passage from the patient's nose to his own skin, whence it is driven into the wound at the time of injury.

These two microbes are the main sources of infection, for apart from the staphylococci on his own skin, the worker's immediate environment contains few infecting bacteria that might enter at the time of injury.

The Effect of Infection on the Wound

It is well known that obvious sepsis delays the healing of a wound, and may result in permanent disabilities. However, the survey also revealed a high incidence of infection in clinically healthy wounds. This "silent" infection is dangerous as a concealed source of infection for other wounds, and it may delay healing to some extent.

Prevention and Treatment of Wound Infection

Practicable means of preventing wound infection include removal or killing of the bacteria that have been implanted at the time of injury, and protection of the wound from external bacteria, by using aseptic techniques of wound dressing and by applying occlusive dressings, or by ensuring the presence of actively antibacterial agents, during the whole period of treatment of the wound.

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Comparative tests, mainly upon minor lacerations and compound fractures of the terminal bones of the fingers, have shown that thorough cleansing of the wound and surrounding skin reduces the infection rate. However, the cleansing agents in common use appear to act chiefly as mechanical removers of the bacteria, and little by reason of any antibacterial powers they may have.

The introduction into the wound of a single dose of penicillin and sulphathiazole, sulphathiazole alone, or sulphathiazole and proflavine, at the time of its first operative cleansing, hardly affects the infection rate; repeated local applications of sulphathiazole and proflavine reduce the infection rate to some extent.

In this connection, it may be mentioned that controlled tests on *established* septic lesions of the hand, made partly in collaboration with Lady Florey (p. 79), showed quite clearly the enormous benefit from penicillin treatment, both in the final result of the treatment and in the acceleration of healing.

Aseptic measures.—The early experience of the war emphasised the inadequacy of current aseptic measures in combating wound infection arising from bacteria added during the treatment of the wound. The high added-infection rates observed in war wounds held also for industrial injuries; infection may be acquired in the factory surgeries, in outpatient departments, and in the hospital wards. In all three places, however, a revision of the aseptic techniques without doubt reduced the incidence of added infection. For example, a revision not only of the dressing technique, but also the design and lay-out of the outpatient department, was followed by a ten-fold reduction in the frequency of added streptococcal infection. In many cases more stringent aseptic precautions can be imposed without increase in the work of dressing, by redesign of the dressing room and "rationalisation" of the dressing procedure.

With the risk of added infection of a wound during its exposure for treatment reduced to a minimum, there remains the provision of a wound cover that is impervious to bacteria. This is particularly important in the factory, where the ordinary bandage is liable to become displaced or soaked in oil, lubricating fluid, etc. A plastic occlusive outer dressing which was tried did not, however, produce any observable reduction in the infection rate.

Prevention of wounding.—Of all the small wounds of the hand incurred in a light engineering factory, whether requiring treatment or not, the proportion that became septic was of the order of 1-2 per cent. Current factory propaganda urges all workers to attend factory surgeries on wounding; but since each worker on the average wounds himself, at least trivially, once every ten days, the success of such propaganda in a factory of 5,000 workers would not only overwhelm the medical services, but would dislocate the manufacturing processes. Nevertheless, since the sepsis that does occur may be serious, much might be done for the prophylaxis of wound infection by measures that minimise the risk of wounding, as by arranging for the automatic disposal of swarf and by reducing awkward features on machinery.

Miscellaneous Laboratory Investigations

During the course of the epidemiological and clinical work, various laboratory methods were perfected, including coagulase and haemolysin tests for staphylococci, the use of penicillinase in routine cultures, and the determination of sulphonamide sensitivity of different organisms.

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B. CADNESS-GRAVES, R. WILLIAMS, G. J. HARPER and A. A. MILES—
Slide-test for coagulase-positive staphylococci. *Lancet*, 1943, **i**, 736.

B. CLAYTON-COOPER and R. E. O. WILLIAMS—
Added infection in industrial wounds. *Brit. J. industr. Med.*, 1945, **2**, 146.

M. E. FLOREY and R. E. O. WILLIAMS—
Hand infections treated with penicillin. *Lancet*, 1944, **i**, 73.

W. GISSANE, A. A. MILES and R. E. O. WILLIAMS—
Design of dressing stations and control of wound infection. *Brit. J. industr. Med.*, 1944, **1**, 90.

G. J. HARPER—
Inhibition of penicillin in routine culture media. *Lancet*, 1943, **ii**, 569.

G. J. HARPER and W. C. CAWSTON—
The in vitro determination of the sulphonamide sensitivity of bacteria. *J. Path. Bact.*, 1945, **57**, 59.
A selective medium for the detection of *Ps.pyocyanea* in wounds infected with *Proteus vulgaris*. *Bull. Inst. med. lab. Tech.*, 1945, **11**, 40.

A. A. MILES—
Epidemiology of wound infection. *Lancet*, 1944, **i**, 809.

A. A. MILES, *et al.*—
Hospital infection of war wounds. *Brit. med. J.*, 1940, **ii**, 855 and 895.

A. A. MILES, R. E. O. WILLIAMS and B. CLAYTON-COOPER—
The carriage of *Staphylococcus* (*pyogenes*) *aureus* in man and its relation to wound infection. *J. Path. Bact.*, 1944, **56**, 513.

H. SCHWABACHER, A. C. CUNLIFFE, R. E. O. WILLIAMS and G. J. HARPER—
Hyaluronidase production by staphylococci. *Brit. J. exp. Path.*, 1945, **26**, 124.

R. E. O. WILLIAMS—
Applicator for penicillin cream. *Lancet*, 1945, **ii**, 306.
Skin and nose carriage of bacteriophage types of *Staph. aureus*. *J. Path. Bact.*, 1946, **58**, 259.

R. E. O. WILLIAMS and E. H. CAPEL—
The incidence of sepsis in industrial wounds. *Brit. J. industr. Med.*, 1945, **2**, 217.

R. WILLIAMS, B. CLAYTON-COOPER, J. McK. DUNCAN and E. M. MILES—
Observations on CTAB (Cetavlon); its use in surgery. *Lancet*, 1943, **i**, 522.

R. E. O. WILLIAMS, B. CLAYTON-COOPER, H. C. FAULKNER and H. E. THOMAS—
Further observations on the use of Cetavlon (CTAB) in surgery. *Lancet*, 1944, **i**, 787.

R. E. O. WILLIAMS, B. CLAYTON-COOPER, T. W. HOWAT and A. A. MILES—
The control of hospital infection of wounds. *Brit. J. Surg.*, 1945, **32**, 425.

R. E. O. WILLIAMS and G. J. HARPER—
The frequency of haemolytic streptococci of different groups in the normal nose and throat. *Mon. Bull. Min. Hlth, Lond.*, 1944, **3**, 86.
Determination of coagulase and alpha-haemolysin production by staphylococci. *Brit. J. exp. Path.*, 1946, **27**, 72.
Staphylococcal haemolysis on sheep blood agar, with evidence for a fourth haemolysin. *J. Path. Bact.*, 1947, **59**, 69.

R. E. O. WILLIAMS and A. A. MILES—
The bacterial flora of wounds and septic lesions of the hand. *J. Path. Bact.*, 1945, **57**, 27.

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The Burns Research Unit

Royal Infirmary, Glasgow, 1942–43

Birmingham Accident Hospital and Rehabilitation Centre, since 1944

Staff:—

Leonard Colebrook, M.B., F.R.C.O.G., F.R.S. (*Director*).

Temporary staff and attached workers:—

At Glasgow:

T. Gibson, M.B., F.R.C.S.E.
A. Brown, M.B., M.R.C.P.E., F.R.F.P.S.G. (*part-time*).
Miss E. Semeonoff, B.Sc.

At Birmingham:

J. M. Duncan, M.B.
Miss E. Semeonoff, B.Sc. (*till March, 1945*).
J. W. Keyser, M.Sc., A.R.I.C. (*from March, 1945*).

As mentioned on p. 29, Dr. Leonard Colebrook, of the Council's scientific staff, was seconded to the R.A.M.C. soon after the outbreak of war. He served as Consulting Bacteriologist, with the rank of Colonel, until 1942. In that capacity he had a prominent part in establishing the uses and limitations of sulphonamide drugs for the local prophylaxis and treatment of wound infections. Some of his work while in the Army has been noticed on pp. 34-35; relevant publications are listed below.

In relation to the programme of work of the Burns Sub-Committee (pp. 44-46), Dr. Colebrook was released from the Army at the Council's request in 1942 to direct a Burns Research Unit. By arrangement between the Council and the Managers of the Royal Infirmary, Glasgow, the Unit was established during 1942 and 1943 in the burns wards of that hospital in the clinical charge of Mr. A. M. Clark, where very large numbers of civilian patients with industrial and other accidental burns are admitted annually. Mr. Gibson was appointed by the Council as whole-time temporary assistant to Mr. Clark in the surgical part of the work, and Dr. Colebrook directed the laboratory studies, co-ordinating these with the clinical observations. Professor J. W. S. Blacklock, Pathologist to the Royal Infirmary, kindly arranged laboratory facilities for Dr. Colebrook and his team, and himself supervised the pathological investigations. Dr. Brown was given a part-time grant for haematological studies, and to undertake the general medical care of the patients. Others who co-operated in the studies of the Unit at Glasgow were Dr. J. P. Todd, Professor of Pharmacy at the Royal Technical College, Glasgow, and Dr. A. B. Anderson, Biochemist to the Royal Infirmary; Dr. Anderson supervised the work of Miss Semeonoff, who received a grant from the Council.

The chief problems studied by the Unit, both at Glasgow and subsequently at Birmingham, have been the control of infection in burns and scalds, and the treatment of " burns shock " by fluid replacement. The investigations which led to the development of a first-aid cream for burns have been mentioned on p. 46. A full account of the principal researches undertaken by the Unit at Glasgow was published as the Council's *Special Report Series* No. 249 in 1944. By adopting strict precautions in the performance of dressings, and by the use of a cream containing penicillin and a sulphonamide drug for the elimination of streptococci, it was possible greatly to reduce the incidence of severe infection in burns and scalds, but a factor limiting success during the

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work at Glasgow was that the dressings were carried out in open wards, where the air was frequently polluted by streptococci.

In 1944 the opportunity occurred to transfer the work to Birmingham, where, also, there were large numbers of industrial burns requiring treatment, and where—in the Accident Hospital and Rehabilitation Centre, of which Mr. W. Gissane is Clinical Director—provision could be made for doing all the dressings of burned cases in a specially air-conditioned room. This plan, together with still more strict care in the dressing procedures, and the continued use of penicillin by local application, has almost entirely eliminated the occurrence of "hospital" infections by haemolytic streptococci and *Ps. pyocyanea.*

In the course of investigations made at Birmingham with Dr. Bourdillon (p. 215), conclusive evidence has come to hand of the remarkable scatter of air-borne microbes which commonly occurs whenever surgical dressings are disturbed or beds are made. These observations—in which the Bourdillon slit-sampler (p. 214) was used—have thrown new light on the mechanism of hospital cross-infections; and it has been made clear that pollution of the air of operating theatres and surgical dressing rooms can be dealt with effectively and quickly by mechanical replacement with a free flow of filtered air. This method offers certain advantages over sterilisation by aerosols or ultra-violet radiation, and it should have many important practical applications.

In the treatment of "burns shock," the great value of fluid replacement by plasma transfusions, carefully regulated by measurements of haemoconcentration, has been amply confirmed.

Since the Unit moved to Birmingham, Mr. Garfield Thomas, M.Sc., has received an honorarium to supervise the biochemical aspects of the research.

R. B. Bourdillon and L. Colebrook—
Air hygiene in dressing-rooms for burns or major wounds. *Lancet,* 1946, **i,** 561 and 601.

A. Brown, E. Lewis-Faning and M. M. Whittet—
Some social aspects of burns in Glasgow. *Brit. med. J.,* 1945, **i,** 144.

W. C. Cawston and L. Colebrook—
Inhibition of Proteus in cultures from wounds. (Letter.) *Lancet,* 1943, **ii,** 240.

A. M. Clark, L. Colebrook, T. Gibson, M. L. Thomson and A. Foster—
Penicillin and propamidine in burns; elimination of haemolytic streptococci and staphylococci. *Lancet,* 1943, **i,** 605.

L. Colebrook—
Treatment of war wounds by sulphonamide packs. *Lancet,* 1940, **ii,** 113.
Sulphanilamide and wound infections. (Letter). *Brit. med. J.,* 1940, **ii,** 682.
Contribution to "Discussion on chemotherapy and wound infection". *Proc. R. Soc. Med.,* 1941, **34,** 337.
The disinfection of skin. *Bull. War Med.,* 1941, **2,** 73.
Sulphonamide resistance. (Letter.) *Lancet,* 1943, **ii,** 207.
First aid for thermal burns and scalds. (Letter.) *Brit. med. J.,* 1944, **i,** 342.
A Burns Unit at the Birmingham Accident Hospital and Rehabilitation Centre. *Nursing Times,* 1945, **41,** 4.

L. Colebrook and W. C. Cawston—
Are the sulphonamides merely bacteriostatic agents? *Lancet,* 1945, **i,** 394.

L. Colebrook, S. D. Elliott, W. R. Maxted, C. W. Morley and M. Mortell—
Infection by non-haemolytic group-A streptococci. *Lancet,* 1942, **ii,** 30.

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L. COLEBROOK and A. E. FRANCIS—
Elimination of streptococci from superficial wounds by sulphanilamide powder. *Lancet*, 1941, **i**, 271.
Varying sensitivity of haemolytic streptococci to the sulphonamides. *J. Path. Bact.*, 1941, **53**, 155.

L. COLEBROOK, T. GIBSON and J. P. TODD—
First-aid treatment of burns and scalds. *Brit. J. industr. Med.*, 1944, **1**, 99.

L. COLEBROOK, T. GIBSON, J. P. TODD, A. M. CLARK, A. BROWN, A. B. ANDERSON and E. SEMEONOFF—
Studies of burns and scalds. (Reports of the Burns Unit, Royal Infirmary, Glasgow, 1942–43.) *Spec. Rep. Ser. Med. Res. Coun., Lond.*, No. 249, 1944.

A. T. FULLER, L. COLEBROOK and W. R. MAXTED—
The mode of action of sulphanilamide. *J. Path. Bact.*, 1940, **51**, 105.

T. GIBSON and P. B. MEDAWAR—
The fate of skin homografts in man. *J. Anat., Lond.*, 1943, **77**, 299.

The Radiotherapeutic Research Unit, Hammersmith Hospital, London

Staff and attached workers (including wartime members of the previous Radium Beam Therapy Research Group—see below):—

Miss Constance A. P. Wood, M.R.C.P., D.M.R.E., F.F.R. (*Director*).
L. G. Grimmett, B.Sc. (*till 1944*).
J. A. V. Fairbrother, B.Sc., Ph.D. (*till 1942*).
F. I. Wright, B.Sc., Ph.D. (*till 1941*).
J. C. Davidson, M.B., D.M.R.E. (*Prophit student, Royal College of Surgeons, 1941-42*).
J. W. Boag, B.Sc. (*since 1942*).
Miss L. Walter, M.B., D.M.R.E. (*Prophit student, Royal College of Surgeons, 1942-45*).
P. Howard Flanders, B.Sc. (*since 1942*).

During the war an important change took place in the organisation of the Radium Beam Therapy Research, which had been in progress since 1934 under successively different administrative arrangements, as outlined in the Council's last seven Annual Reports. As the scope of the research came to include studies in the treatment of cancer by deep X-rays as well as by radium beam therapy, the original name became inappropriate, and in 1941 the team of workers was reconstituted as the Council's Radiotherapeutic Research Unit. Dr. Constance Wood, who had been the chief radium therapist from the beginning of the work, was appointed Director of the Unit; she serves the Council on a half-time basis in this capacity, while also holding the post of radiotherapist in the service of the London County Council at the Hammersmith Hospital, where the Unit has been established since January, 1942.

During the war, also, changes took place in the ownership of the large quantity of radium used for the beam therapy work. Formerly, the greater part of this radium ($8\frac{3}{4}$ grammes) was held on loan from the Union Minière du Haut Katanga (Radium Belge) through the Chemical Service Co. Ltd. In 1942-43 this radium was purchased by the National Radium Trust, and it has since been generously lent to the Council by the Radium Commission, who have also lent further smaller quantities for the purposes of the Unit's work. An additional gramme of radium, previously lent to the Council by the Royal College of Surgeons, has since been purchased by the Trust for loan on the same basis.

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The brief account of the research work done by the team during the war years, which is given below, includes studies made both before and after the establishment of the Radiotherapeutic Research Unit.

On the outbreak of war, treatment of patients by the radium beam therapy research group came virtually to a standstill. In accordance with the security recommendations, all the radium used for the research—approximately 11 grammes—was placed for safe keeping in a radium borehole; most of the members of the group entered either the Forces or the Emergency Medical Service, and in-patient facilities at the Radium Institute, London, where the work was then accommodated, ceased to be available. However, an attempt was made to keep in touch with all patients formerly treated, and, during 1940, it was possible to see them at the Radium Institute.

In the latter part of 1940 the quarters occupied in the Radium Institute were damaged by enemy action. Records and some of the group's equipment were then placed in store, while the remainder of the equipment, including the X-ray outfit, was moved to the Imperial College of Science and Technology at South Kensington, where hospitality was kindly provided in the Physics Department. Here work was continued on the exact matching of the dose distribution from the X-ray set with that from the radium beam unit; work was also carried out on the development of wavelength-independent material for the construction of moulded ionisation chambers for measuring X-radiation, and preliminary designs were made for a van de Graaff electrostatic generator.

At the end of 1941, agreement was reached between the Council and the London County Council for the accommodation of the Radiotherapeutic Research Unit at the Hammersmith Hospital, and for the provision of in-patient facilities in the hospital. Early in 1942, the necessary structural alterations were completed, and treatment of patients at Hammersmith was begun. A new radium borehole was made at the hospital, and, in November, 1942, the radium for the beam therapy work was transferred to it.

Experimental Comparison between Gamma Rays and X-rays

A comparison was made between the results of treatment in two series of cases of cancer of the mouth and throat, one series being treated by gamma rays from a ten-gramme radium beam unit and the other by X-rays from a 200 kV X-ray apparatus. The X-ray apparatus was modified in such a way as to obtain matching, as far as possible, of the isodose curves of the radium and X-ray beams, so that the only variable in the experiment should be that of wavelength. In the histological aspects of this work valuable co-operation was received from Dr. F. G. Spear, of the Council's staff, and his colleague Dr. A. Glücksmann, at the Strangeways Research Laboratory, Cambridge (p. 335). A full report of the experiment has since been prepared for publication.

Developments in the Technique of Treatment

An instrument has been designed with which it is possible to determine the isodose contours for three perpendicular planes passing through a tumour. The process is rapid enough to be used on patients under treatment, and is of great assistance in planning the best arrangement of fields of exposure to radiotherapy. A treatment caliper was also designed and constructed; this instrument increases the accuracy with which the radiation beam can be directed at a tumour during treatment. In addition, a celluloid model of the human body was built for the measurement of the total energy absorption in a patient during treatment; with this model the absorption which occurs in conventional X-ray therapy technique has been investigated.

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Electrostatic X-ray and Neutron Generator

In collaboration with workers at the Imperial College of Science and Technology, South Kensington, much progress has been made in the design and construction of a high voltage electrostatic generator. The machine has been erected at Hammersmith Hospital, and is now almost complete. It is proposed to use it for biophysical research on cancer.

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A dose contour finder for symmetrical and unsymmetrical radiation beams. *Brit. J. Radiol.*, 1943, **16**, 314.

C. A. P. Wood—
Teleradium therapy in wartime. *Proc. Soc. Radiotherapists*, 16th March, 1940.
Technique of teleradium treatment. *Proc. R. Soc. Med.*, 1943, **36**, 263.

The Department of Experimental Medicine, Cambridge

Staff:—

Professor R. A. McCance, M.D., Ph.D., F.R.C.P. (*Director*).
Miss E. M. Widdowson, B.Sc., Ph.D.

Attached workers:—

R. F. A. Dean, M.R.C.S., L.R.C.P.
Miss E. Wilkinson, B.Sc.
Miss C. M. Walsham, B.Sc.

The Department was established by the Council, jointly with the University of Cambridge, towards the end of the period under review, but Dr. McCance and Dr. Widdowson, who has been a member of the Council's staff since 1941, had been actively engaged in research on the Council's behalf throughout the war. They have had the assistance from time to time of the following: Dr. Winifred F. Young, Dr. D. A. K. Black, Miss B. K. Alington, Dr. N. L. Kent, Miss C. N. Edgecombe, Miss C. M. Walsham, Miss E. Wilkinson, Dr. Margery Cutting and Dr. R. F. A. Dean. Dr. Black and Dr. Cutting held Beit Memorial Fellowships; the others were paid by the Council.

Several of the investigations made by Dr. McCance and his colleagues during the war years have been reviewed earlier in this Report (pp. 17, 98 and 100). Some of their other researches during the period covered are briefly summarised below.

While engaged upon their experimental study of rationing (p. 98), Dr. McCance and Dr. Widdowson noticed that the volunteers on the test diets were not absorbing calcium so satisfactorily as they had been doing on their normal diets, and an elaborate series of studies was instituted to explore this question. Eight persons took part in these experiments in human nutrition, and the work involved a very rigid discipline over a period of nearly nine months. It was conclusively shown that calcium is absorbed much less freely from brown bread than from white. On the basis of the earlier experiments of Harrison and Mellanby on the rachitogenic action of phytic acid for dogs, it seemed likely that the substance in brown bread which interfered with the absorption of calcium was phytic acid, and this

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was subsequently proved to be the case. Phytic acid inhibits the absorption of calcium by forming insoluble calcium salts; it was also shown to be capable under certain conditions of inhibiting the absorption of iron. The investigations of Harrison and Mellanby in dogs and of Dr. McCance and his colleagues in human subjects, on the effect of phytic acid on calcium metabolism, had a very important bearing on the Government's wartime food policy in that they led to the decision to fortify the National Flour with calcium. It is interesting to note that work on similar problems, leading to almost identical conclusions was carried out independently in Denmark during the war.

Dr. Widdowson has been responsible for a number of dietary studies by the individual method on selected groups of children and adults. An account of her pre-war investigations of the individual diets of large numbers of children in different economic circumstances has been published in the Council's *Special Report Series*. Similar studies made on groups of school children and others during the later years of the war established the correctness, in the light of subsequent experience, of some of the predictions based on the experimental study of rationing mentioned above. One of the interesting findings resulting from these surveys is that boys at some boarding schools grow very much more rapidly during the holidays than during the term.

At the beginning of the war Dr. McCance and Dr. Young were engaged upon studies of the physiology of infancy, and particularly of the renal function of very young children; this fundamental work was continued, as opportunity offered, throughout the war. It has been shown that the kidney is a relatively inefficient organ for some time after birth, and this has explained a number of well recognised difficulties in the management of premature and full-term children. The work has emphasised the dangers of allowing a child to become dehydrated, and at the same time has shown how unwise it is to administer saline solutions indiscriminately. Miss Wilkinson has extended these observations to animals and has shown that their kidneys are subject to the same limitations as those of man, although there are naturally certain differences between each species. Based upon these studies, satisfactory methods have been evolved for the treatment of dehydrated children, and Dr. Dean and Dr. McCance have now begun to examine other aspects of the problem. These investigations have underlined the fact that the physiology of the infant is inherently different from the physiology of the adult, and that a knowledge of its special features is essential for work in paediatrics.

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The excretion of urea, salts, and water during periods of hydropaenia in man. *J. Physiol.*, 1945, **104**, 196.

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R. A. McCance and E. M. Widdowson—
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The absorption and excretion of zinc. *Biochem. J.*, 1942, **36**, 692.
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Mineral metabolism. *Ann. Rev. Biochem.*, 1944, **13**, 315.
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The secretion of urine during dehydration and rehydration. *Ibid.*, 1944, **102**, 415.
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E. M. Widdowson and B. K. Alington—
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The war and school-boys' food. *Ibid.*, 1942, **ii**, 689.
Growth at home and at school. *Ibid.*, 1944, **ii**, 152.

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D. C. WILSON and E. M. WIDDOWSON—
A comparative nutritional survey of various Indian communities. *Indian med. Res. Mem.*, 1942, No. 34.

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W. F. YOUNG and R. A. MCCANCE—
The secretion of urine by dehydrated and normal infants. *Arch. Dis. Childh.*, 1942, **17**, 65.

NUTRITION

The Nutrition Building, Mill Hill

Staff and attached workers:—

Sir Edward Mellanby, K.C.B., M.D., Sc.D., F.R.C.P., F.R.S.
Lady Mellanby, D.Sc.
J. D. King, Ph.D., L.D.S. (*on Active Service during part of the war*).
B. S. Platt, C.M.G., M.Sc., Ph.D., M.B. (*1940-42*).
Miss G. E. Glock, M.Sc. (*till March 1942*).
Helen Coumoulos, D.D.S. (Athens), Ph.D. (*British Council Scholar*).

Associated worker (at Sheffield):—

Helen Mellanby, Ph.D., M.B.

During 1939, most of the research work on nutrition by Sir Edward and Lady Mellanby, which had been continuously in progress at the Field Laboratory of the University of Sheffield since 1921, was transferred to temporary premises at the Farm Laboratories of the National Institute for Medical Research at Mill Hill. In 1940 the new Nutrition Building, erected by the Council for their research, was completed and all work, both at Sheffield and the temporary laboratory, was moved there.

Dr. J. D. King and Dr. Helen Mellanby continued their investigations of dental disease at the Field Laboratory, Sheffield, until early in 1940, when Dr. King joined the Army Dental Corps, and for a year spent much of his time in studying the problem of gingivitis (paradontal disease) in the Army. In 1941 it was decided that more fundamental research on this problem was necessary, and Captain King was seconded to the Council's service to make these studies.

In 1940 Dr. B. S. Platt, of the Council's staff, who, for several years had been making an extended survey of nutritional and allied conditions in Nyasaland (p. 103), returned to this country. With Miss Glock, he made a number of investigations at the Nutrition Building, Mill Hill. Later, his studies were transferred to the National Hospital for Nervous Diseases, London, and in 1944 he was appointed Director of the Council's Human Nutrition Research Unit, housed temporarily at that hospital. His publications during the war period, including those resulting from his studies at Mill Hill, are listed on pp. 285-6.

Effect of Phytic Acid on Calcium Absorption

In 1939 Sir Edward Mellanby, in association with Professor D. C. Harrison of Belfast University, published an account of work on which they had been engaged for several years, which showed that phytic acid was the

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chief rickets-producing substance in cereals. The presence of such a substance, especially in oatmeal, was established by Mellanby as long ago as 1922, and the responsible agent has been referred to in some previous reports as the rachitogenic toxamin, i.e. a substance in food which actively produces rickets, and the effect of which can be antagonised by vitamin D. It was found in this work that:—

(*a*) phytic acid (inositol hexaphosphoric acid) and neutral sodium phytate, prepared from commercial phytin, exerted powerful rickets-producing actions when added to a non-rachitogenic or slightly rachitogenic diet;

(*b*) the degree of rachitogenic activity shown by these compounds was roughly comparable with that shown by oatmeal when given in an amount equivalent as regards phytic acid phosphorus;

(*c*) the phytic acid phosphorus fraction extracted from oatmeal itself showed the same rachitogenic action, and purified sodium phytate prepared from this fraction was equally potent;

(*d*) the rachitogenic action of sodium phytate, as of cereals, was antagonised by adding extra calcium to the diet, and commercial phytin (calcium-magnesium phytate) was slightly antirachitic.

Evidence was given suggesting that the rickets-producing action of cereals is normally due not, as had been previously thought, to the unavailability of their phosphorus, but to the action of the phytic acid in inhibiting the absorption of calcium from the alimentary canal. The amount of phytic acid in oatmeal is approximately twice that required to precipitate the calcium of the cereal at neutrality, and it was postulated that the phytic acid exerts its rachitogenic action by preventing absorption of the calcium of the cereal itself and of further amounts of calcium from the rest of the diet.

Since the publication of this work in 1939, Sir Edward Mellanby has continued his investigations on phytic acid as an anti-calcifying substance, and has shown that, even in the presence of vitamin D, phytic acid has an inhibitory effect on calcium absorption from the gut. Under this condition inorganic phosphate, unlike phytate, has but little anti-calcifying effect. When, however, there is little or no vitamin D in the food and in the body, both phosphate and phytate strongly interfere with calcium absorption. He has also shown that vitamin D causes an increase in the destruction of phytic acid in the alimentary canal.

It is clear that these discoveries of the effect of phytic acid, announced in 1939, were just in time to lead to important applications when Government action in regard to the nation's bread supply became necessary in the war. Mellanby had shown in 1925 that brown flour has a larger rickets-producing effect in experimental animals than white flour, and the discovery of the action of phytic acid on calcification cleared up this part of the problem. Dr. McCance and Dr. Widdowson (p. 274) made a valuable contribution to the subject by showing that phytic acid also interfered with calcium absorption in man. On the basis of all these investigations a decision was ultimately taken to add calcium carbonate to the National Flour (7 oz., later 14 oz., of *creta praeparata* to 280 lb. of the flour). There is every reason to believe that this is one of the nutritional changes which, in spite of the austerity and meagreness of wartime diets, has brought about the great improvement in public health as measured by morbidity and mortality statistics since 1939.

Bony and Nervous Changes following Vitamin A Deficiency in Young Animals

It was reported in 1939 that Sir Edward Mellanby had demonstrated the destruction of the cochlear division of the 8th nerve and, to a lesser extent,

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of its vestibular division, by overgrowth of periosteal bone of the labyrinth, induced by a deficiency of vitamin A in young dogs. This work has been developed, and was summarised to date in the Croonian Lecture of the Royal Society in 1943. It was shown that, under these conditions, abnormal growth takes place in many bones in close proximity to the nervous system; those bones which usually grow most during the experimental feeding period show the greatest abnormalities, and the effect of this dysplasia is disastrous both to the peripheral and central nervous systems, primarily on the afferent side. Such degenerative changes in vitamin A deficiency as destruction of the trigeminal, the olfactory and the auditory nerves, and the posterior roots of the cervical region of the cord, can be traced to pressure of excessive bone, largely on the ganglion cells of the nerves. Degeneration of endogenous fibres in the cord, such as the spino-cerebellar tracts, is also associated with the abnormal bone growth of vitamin A deficiency.

Further studies of bone dysplasia due to vitamin A deficiency have revealed a new function of the vitamin, in that it controls, directly or indirectly, the position of action in growing bone of osteoblasts and osteoclasts. Thus, surfaces on which deposition of bone by osteoblasts would normally take place may, in vitamin A deficiency, show either absence of osteoblasts or their replacement by osteoclasts. Similarly, surfaces of such growing bone, normally being absorbed by osteoclastic activity (e.g. the surfaces of vertebrae nearest the spinal cord), may show very few osteoclasts in vitamin A deficiency. When these abnormal forms of bone growth are established in young animals, addition of vitamin A to the diet rapidly brings about a reversal of cell activity to the normal positions. This reaction is usually excessive, as if a great effort were being made to restore the bone to its proper shape. The restorative process on adding vitamin A seems to follow even if the adjacent nervous tissue has been destroyed by the bone dysplasia. The shape and texture of many bones other than those in close proximity to the nervous system, including the pelvis and long bones, are affected by deficiency of this vitamin.

Inco-ordination and bone dysplasia have also been demonstrated in rabbits, ferrets, rats and chicks maintained on vitamin A deficient diets.

It is of interest to note that both participants of the original vitamin A complex, vitamin D and vitamin A itself, have been shown to be concerned with the growth of bone, vitamin D controlling its calcification, vitamin A its shape and texture.

Canine Hysteria

Sir Edward Mellanby's recent work on the relation of " agenized " flour to the causation of canine hysteria was published after the end of the period under review, and will be discussed in the Council's next Report.

Dental Disease

The work of Lady Mellanby on dental problems, which had been begun with support from the Council as long ago as 1917, had indicated that the teeth of the British population were commonly defective in structure, and that the condition known as hypoplasia (" M-hypoplasia " as opposed to the " text-book " or gross variety) was very extensive throughout the country. Animal experiments proved that this form of hypoplasia was due to a dietetic defect, and especially to a subnormal intake of vitamin D and calcium in the diet in relation to the amount of cereal. Hypoplastic teeth in man had been shown to be more prone to decay than teeth of good strucure. Moreover,

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apart from its effect on structure, the type of diet which produced good teeth resulted in delayed onset, and in the arrest, of active caries.

For some years before the recent war the consumption of milk, eggs, cod-liver oil and other vitamin D-containing substances by pregnant and nursing women and young children had been gradually increasing, and further great improvements in this direction were effected during the war years. Moreover, early in 1940 vitamins D and A were added to all margarines, and in 1943 calcium carbonate was added to all flours. On the basis of Lady Mellanby's previous investigations it seemed likely that the influence of such dietetic changes would be reflected in a better structure of children's teeth, and a lessened incidence of caries. With the idea of testing this hypothesis, she, in association with Dr. Helen Coumoulos, who worked with the aid of a scholarship from the British Council, made an extensive investigation in 1943 of the condition of the teeth of children aged five who attended elementary schools under the control of the London County Council. The individual teeth of over 1,800 such children were charted for structure, caries and other conditions. Children of the same age-group in most of these schools had been examined by Lady Mellanby from the same point of view in 1929, and it was possible, therefore, to make an estimate of any change in the dental structure and incidence of caries that had taken place in the meantime. The outcome was gratifying, since it was shown in 1943 that 22 per cent. of the children were, according to the standards used, " caries-free ", as compared with under 5 per cent. in 1929. The structure of the teeth of the children examined in 1943 was also greatly improved, 19 per cent. of them having teeth of perfect or nearly perfect structure, compared with only 8 per cent. in 1929; again, only 33 per cent. had very defectively formed teeth in 1943 compared with 58 per cent. in 1929. From every point of view, therefore, there had been a great improvement in the condition of the teeth of young children in the intervening years.

In 1945 Lady Mellanby and Dr. Coumoulos repeated the study and found that, during the interval of twenty months on the average, there had been a further improvement in the dental condition of comparable groups of 5-year-old children. Thus, in 1945 the " caries-free " group had risen from 22 to 26.5 per cent. and the percentage with teeth of good structure had also increased.

A further point of interest in this work was the large increase in the number of teeth showing the arrest of caries. Thus, whereas in 1943 11.7 per cent. of the carious teeth present showed arrest, this figure had increased in 1945 to 21.5 per cent., indicating a beneficial effect of some powerful post-eruptive influence. It will be seen that all the results obtained in this survey again indicated a definite improvement in the dental condition of 5-year-old children attending L.C.C. schools.

Lady Mellanby has continued her efforts to elucidate the action of certain other dietetic factors on tooth structure. It has been shown that when the consumption of vitamin D is low, phytic acid, or foods rich in phytic acid, interfere both with the structure of the dental tissues and with the amount of dentine laid down. This is true also when the calcium-phosphorus ratio of the diet remains unaltered. Even with larger, but still inadequate, amounts of the vitamin in the diet, phytic acid reduces the amount and thickness of dentine laid down, though it does not harm its minute structure.

Miss G. E. Glock, Dr. Helen Mellanby, Lady Mellanby, Dr. Margaret M. Murray and Dr. J. Thewlis studied histologically, by chemical analysis and by X-rays, the different stages in the enamel development of the teeth of

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puppies on diets varying in their vitamins A and D content. When cod-liver oil was included in the diet, calcification of the enamel progressed more rapidly than in control animals receiving a diet deficient in vitamins A and D.

Dr. Coumoulos made a field survey of the dental condition of some five thousand 5-year-old elementary school children in various parts of England, and of a few in Wales, as well as of large numbers of children of other age groups. The teeth of the children of Maldon, Essex, where there is much fluorine in the water, were found to be the best in structure and the least carious of those in all the groups examined. A summary of some of the data obtained in this survey has been published.

During the early part of the war, Dr. King completed his work on the effect of vitamin A deficiency on the gingivae of rats, and a preliminary report was published on the treatment of " trench mouth " in man by nicotinic acid therapy. The latter study was continued on a larger scale in the Army, and extended to various groups of children. In general, it was concluded that the *ulcerative* syndrome was associated with two main aetiological factors—local trauma in the mouth and general depressed tissue resistance—as a result of which fusospirochaetal and other anaerobic micro-organisms were enabled to proliferate unduly and to contribute to the production of the characteristic necrosis of the gingivae and other structures.

Early in 1942 a form of *non-ulcerative* gingivitis was found in a stock colony of ferrets, and it was noted that these lesions bore a remarkable resemblance to many of those occurring in the human mouth. They arose in the parts of the gum which were nearest to the opening of the salivary ducts, and were accompanied by deposition of tartar on the adjacent teeth. As the disease progressed the calculus increased in amount and the gingivae became more swollen and haemorrhagic. The later phases included gingival atrophy, resorption of the alveolar bone, " erosion " of the cementum or the dentine of the tooth-roots or both, parodontal abscesses, and loosening of the teeth, but general systemic changes were absent. It was proved by experiment that the gingivitis arose as a direct result of the deposition of tartar upon the teeth, and was, in fact, due to absence of adequate friction of the teeth-surfaces by the food taken into the mouth. Reinforcement of the diet with liberal supplies of vitamins A, the B-complex, C and D, and with mineral salts, with milk, meat, periosteum, bone-marrow and crushed whole bone, or with fresh liver, failed to prevent tartar deposits and gingivitis; nor did alteration of the *p*H of the drinking water have any beneficial effect. On the other hand, addition to the diet of short lengths of whole bone—provided that some muscular, tendinous and periosteal attachments were left *in situ*—prevented deposition of tartar and gingivitis and, respectively, removed and cured these conditions in an established case. The importance of the muscular and other bone attachments lay in their being the main inducement to gnawing of the bone by the animals—hence providing vigorous friction of the tooth and gum surfaces. It was also noted that the enamel cuticle (Nasmyth's membrane) played an important part in tartar formation in ferrets, and, indeed, there was some evidence that presence of this cuticle was one of the prerequisites for deposition of dental calculus. As a direct result of the laboratory studies, preliminary investigations have demonstrated the beneficial effects of frictional therapy in human gum disease, the friction of tooth-surface and gingivae being supplied in this instance by the gnawing of pieces of coarse-fibred sugar cane.

In the course of the investigations in ferrets a technique for examination and photomicrography of the gingival capillaries *in vivo* was also developed,

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with the ultimate aim that it might help in the more accurate assessment of gum conditions in man. For this purpose a capillary microscope, designed by Mr. J. Smiles and Dr. E. J. H. Schuster of the Council's staff at the National Institute, was used. After trials in ferrets the technique was successfully applied to man; a series of capillary photomicrographs has been obtained to illustrate the various appearances of the human gingival vessels as health gives way to disease, and gingival capillaroscopy also proved of value in determining the tissue reactions occurring during the treatment of human lesions by gnawing sugar cane.

In parallel with the work of Dr. Coumoulos mentioned above, a clinical survey was made by Dr. King of the incidence and relationship of enamel mottling, M-hypoplasia and dental caries in three groups of children. In general, the incidence of caries and M-hypoplasia was lowest in the Maldon (Essex) group, and in these mottling was most marked and the drinking water contained a relatively high proportion of fluorine. In individual teeth, however, no negative (inverse) association could be traced between enamel mottling and dental caries. A positive association was found between M-hypoplasia and caries.

Dr. King also made an investigation into the effects of daily supplements of boiled sweets and chocolate biscuits on the deciduous teeth of children aged 2-5 years in institutions. The supplements were given at night, immediately before the children went to bed, and after any cleansing of the mouth and teeth. No increase in caries activity was found in the children over periods of six months to two years. A dietary survey by Miss M. W. Grant, B.Sc., revealed a relatively high intake of vitamins A and D and a fairly satisfactory level of calcium and phosphorus. Excluding the experimental supplements, carbohydrates comprised as much as 50 per cent. of the diet, so that the investigation gave no support for the carbohydrate fermentation theory of caries.

Dr. Helen Mellanby carried out experiments on the effect of maternal dietary deficiency of vitamin A on the dental tissues in rats. Females aged 3-4 weeks were fed on the deficient diet, and after periods varying from 12-30 weeks were allowed to breed. The diet produced defects in the mothers' dental tissues, while severe abnormalities were found in all the dental tissues of the young. Control young born from litter-mates receiving the same diet, plus vitamin A, were normal.

While on a visit to Arctic Finland, Dr. Helen Mellanby examined the teeth of 70 Finnish Lapp children for surface structure and caries. M-hypoplasia was present in 75.8 per cent. of deciduous and 93.3 per cent. of the permanent teeth, while some 55.3 per cent. of the deciduous and 44.5 per cent. of the permanent teeth were decayed. The teeth seen in Lapp children's skulls in a Helsinki museum were of much better structure, and showed very little caries, compared with their modern counterparts in present-day Lappland. Great dietetic changes have occurred among the Lapp population in recent years, which can be correlated with their worsened dental condition.

H. Coumoulos—
Dental condition of five-year-old elementary school children. *Nature, Lond.*, 1946, **158**, 559.

G. E. Glock, H. Mellanby, M. Mellanby, M. M. Murray and J. Thewlis—
A study of the development of dental enamel in dogs. *J. dent. Res.*, 1942, **21**, 183.

D. C. Harrison and E. Mellanby—
Phytic acid and the rickets-producing action of cereals. *Biochem. J.*, 1939, **33**, 1660.

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J. D. KING—

Abnormalities in the gingival and sub-gingival tissues due to diets deficient in vitamin A and carotene. *Brit. dent. J.*, 1940, **68**, 349.

Vincent's disease treated with nicotinic acid. *Lancet*, 1940, **ii**, 32.

Nutritional and other factors in " trench mouth ", with special reference to the nicotinic acid component of the vitamin B_2 complex. *Brit. dent. J.*, 1943, **74**, 113, 141, 169.

Treatment of diseases of the gums. Problems in treatment. *Ibid.*, 1943, **75**, 197.

Experimental investigations of parodontal disease: I. The significance of the blood supply in gingival health and disease of the ferret. *Ibid.*, 1944, **77**, 213, 245.

Enamel cuticle (Nasmyth's membrane) and tartar deposition in the ferret. *Nature, Lond.*, 1945, **156**, 572.

Mottled enamel, M-hypoplasia and dental caries. *Dent. Rec.*, 1944, **64**, 102.

Nutritional factors in dental caries and parodontal disease. *Brit. med. Bull.*, 1944, **2**, 222.

Gingival disease in Dundee. *Dent. Rec.*, 1945, **65**, 9, 32, 55.

Influence of nutrition on parodontal health. *Proc. Nutrit. Soc.*, 1945, **3**, 82.

Dental caries: effect of carbohydrate supplements on susceptibility of infants. *Lancet*, 1946, **i**, 646.

J. D. KING, with the assistance of A. B. FRANCKLYN and I. ALLEN—

Gingival disease in Gibraltar evacuee children. *Lancet*, 1944, **i**, 495.

J. D. KING and R. E. GLOVER—

The relative effects of dietary constituents and other factors upon calculus formation and gingival disease in the ferret. *J. Path. Bact.*, 1945, **57**, 353.

E. MELLANBY—

Neurological aspects of the avitaminoses, with special reference to the peripheral nervous system. *III^e Congrès Neurol. Internat., Copenhague. Comptes Rendus*, 1939, p. 797.

Skeletal changes affecting the nervous system produced in young dogs by diets deficient in vitamin A. *J. Physiol.*, 1941, **99**, 467.

The effect of bone dysplasia (overgrowth) on cranial nerves in vitamin A-deficient animals. *Ibid.*, 1943, **101**, 408.

Nutrition in relation to bone growth and the nervous system. *Proc. R. Soc.*, B, 1944, **132**, 28.

Phytic acid and phytase in cereals. (Letter.) *Nature, Lond.*, 1944, **154**, 394.

Nutritional science in medicine. *Brit. med. Bull.*, 1944, **2**, 202.

H. MELLANBY—

The development of teeth in the albino rat. *Brit. dent. J.*, 1939, **66**, 76.

A preliminary note on defective tooth structure in young albino rats as a result of vitamin-A deficiency in the maternal diet. *Ibid.*, 1939, **67**, 187.

Dental hypoplasia and caries among the children of Finnish Lapps. *Brit. med. J.*, 1940, **i**, 682.

The effect of maternal dietary deficiency of vitamin A on dental tissues in rats. *J. dent. Res.*, 1941, **20**, 489.

M. MELLANBY—

Vitamin D. *Endeavour*, 1943, **2**, 73.

M. MELLANBY and H. COUMOULOS.—

The improved dentition of 5-year-old London school-children. A comparison between 1943 and 1929. *Brit. med. J.*, 1944, **i**, 837.

Teeth of 5-year-old London school-children (Second Study). A comparison between 1929, 1943 and 1945 *Ibid.* 1946, **ii**, 565.

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The Human Nutrition Research Unit, National Hospital, Queen Square, London

Staff:—

Professor B. S. Platt, C.M.G., M.Sc., Ph.D., M.B. (*Director*).
R. A. Webb, D.Phil.
J. C. Waterlow, M.D.

Attached workers:—

C. R. C. Heard, M.Sc., D.Phil.
Miss S. D. Habgood, B.Sc.
Mrs. R. Graham, B.Sc. (*paid from Royal Society grant; till Sept. 1944*).
Miss J. Olley, B.Sc. (*paid from Royal Society grant; from Sept. 1944*).

The Human Nutrition Research Unit was established in January, 1944, in temporary quarters at the National Hospital. Many of its studies are concerned with problems of nutrition in the Colonial territories. Reference to some of these, and to other activities of Dr. Platt and his colleagues during the war, has been made in Section V of this Report. Before the Unit was established, Dr. Platt had worked for part of the war period at the Nutrition Building, Mill Hill (p. 277) and he and Dr. Webb were subsequently given accommodation in the Neurological Research Unit at the National Hospital (p. 256), where Dr. Waterlow was also working at that time.

Colonial diets are commonly deficient in B-vitamins, but certain fermented foodstuffs, traditional articles of diet of Colonial peoples, are important sources of these groups of nutrients. The microbiology of one of these foods—Kaffir Beer—has been studied, and estimates made of the amounts of various B-vitamins synthesised during fermentation. Investigations have also been made of the value of food yeast (p. 112) as a source of these nutrients; some trials of food yeast have been organised in Colonial territories, as reported in "Food Yeast: A survey of its nutritive value" (*M.R.C. War Memorandum* No. 16, 1945). In the course of this work, methods have been devised for chemical and microbiological assays of B-vitamins and certain amino-acids.

Two of the most important staple foods of Colonial peoples are rice and maize. Much less is known about the nutritional properties of milled rice and maize than about wheat products. Investigations have been made into the effects of various treatments on the nutritive properties of these grains. Attention is also being given to the nature and importance of those substances which reduce the value of the B-vitamins of rice and maize for man.

Storage and processing of perishable foodstuffs in Colonial territories is a problem of considerable magnitude. A new method has been devised for drying foodstuffs in edible oils under vacuum, which may provide a solution to this difficulty.

Members of the staff of the Unit took part in the investigation at Sheffield of the effects of deprivation of vitamin C on the skin of human volunteers, to which reference has been made on p. 109. Failure in healing of experimental wounds was encountered after prolonged and extreme vitamin C deficiency in the volunteers, and the phenomenon is being further examined in animals. Some preliminary work has been done in the Unit on skin metabolism in wound healing, as a first step to the study of tropical ulcer—a widespread and disabling disease in Colonial territories.

At the request of the Colonial Office, Dr. Platt visited the British West Indies in the winter of 1944-45, to report on the nutritional state of the

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people there. Among the nutritional deficiencies noted was a condition of oedema, frequently associated with liver damage, which occurred in babies fed on diets poor in protein and rich in carbohydrate (B. S. Platt: "Nutrition in the British West Indies." Colonial No. 195, H.M.S.O., London, 1946). Arising out of this survey, a request was received from the Colonial Office for a worker to be sent to the West Indies to examine further the problem of malnutrition and oedema in babies and children, and Dr. Waterlow went to Jamaica for the purpose in the summer of 1945. He found instances there of a type of fatty liver disease, associated with oedema and gross wastage of the skeletal muscles, in infants fed on high carbohydrate, low protein diets as recorded by Dr. Platt. An account of his detailed clinical and pathological studies of the condition in 15 cases observed, with a discussion of the relationship of this type of liver degeneration to others, is being published in the Council's *Special Report Series*. Although the disease, if untreated, appears to have about a 50 per cent. fatality rate, it has been shown that the infants can be restored to health, with normal liver function, if milk is added to the diet—the beneficial effect being attributed to milk protein.

The influence of therapeutic agents on a similar condition in animals is being investigated in the Unit. The metabolic disturbances in the livers of animals receiving diets similar to those producing fatty livers in infants involve the liver phospholipids. The turnover in the liver of this group of substances is being studied after the introduction of radioactive phosphorus (P_{32}) into the animals; at the same time, the relationship of the phospholipids in the nervous system to those in the liver is being examined. A phospholipid containing inositol is being investigated in both the liver and brain, with a view to determining the significance of inositol in the tissues.

Several of the publications listed below record the results of studies made when Dr. Platt was working at the Nutrition Building, Mill Hill (p. 277); some others relate to nutritional surveys made in African territories, and in Newfoundland, which have been mentioned earlier in this Report (pp. 103 and 104).

J. D. Adamson, N. Jolliffe, H. D. Kruse, O. H. Lowry, P. E. Moore, B. S. Platt, W. H. Sebrell, J. W. Tice, F. F. Tisdall, R. M. Wilder and P. C. Zamecnik—
Medical survey of nutrition in Newfoundland. *Canad. Med. Ass. J.*, 1945, **52**, 227.

R. A. Coulson, P. Ellinger, G. E. Glock and B. S. Platt—
The routine chromatography of fluorescent pigments in urine. *Biochem. J.*, 1942, **36**, xix P.

R. A. Coulson, P. Ellinger and B. S. Platt—
The comparative effect on the elimination of fluorescent pigments in human urine of nicotinamide and related compounds. *Biochem. J.*, 1942, **36**, xii P.

P. Ellinger, G. E. Glock and B. S. Platt—
The urinary elimination of fluorescent pigments in animals as a basis for the assay of nicotinamide and related compounds in foodstuffs. *Biochem. J.*, 1942, **36**, xi P.

M. W. Grant and B. S. Platt—
Drying food samples by the solvent method, using isopropyl ether. (Demonstration). *Biochem. J.*, 1945, **39**, ii P.

C. R. C. Heard (introduced by B. S. Platt)—
A critical examination of the estimation of methionine by H_2O_2 oxidation. *Biochem. J.*, 1945, **39**, xlix P.

J. Olley (introduced by B. S. Platt)—
Determination of sulphur in biological material by hydrogenation. (With demonstration). *Biochem. J.*, 1945, **39**, l P.

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B. S. PLATT—

Rice and its importance for human nutrition. *First Report of the Committee on Nutrition in the Colonial Empire*—Part I. Appendix 6, p. 186. H.M.S.O., London, 1939. Cmd. 6050.

Aspects of nutritional research. *Brit. med. Bull.*, 1944, **2**, 204.

Planning for better nutrition in the Colonies. *Imperial Review*, 1945, **12**, 159.

Notes on some cutaneous manifestations of dietary deficiencies. *Brit. Med. Bull.*, 1945, **3**, 179.

Tables of representative values of foods commonly used in tropical countries. *Spec. Rep. Ser. Med. Res. Coun., Lond.*, No. 253, 1945.

B. S. PLATT and members of the Human Nutrition Research Unit of the Medical Research Council—

The dehydration of foodstuffs in edible oils under vacuum. (Demonstration). *Biochem. J.*, 1945, **39**, lii P.

B. S. PLATT and G. E. GLOCK—

The effect of autolysis and of freezing on the "total nicotinic acid" content of skeletal muscle. *Biochem. J.*, 1942, **36**, xv P.

An azo colour reaction for the determination of vitamin B_1 in National flour. *Ibid.*, 1943, **37**, 439.

The estimation of inositol in animal tissues. *Ibid.*, 1943, **37**, 709.

B. S. PLATT and C. R. C. HEARD—

Improvements in and relating to the treatment for preservation and storage of vegetables and other edible material. *Patent Office, London*, Specification No. 13929/44, 1944.

B. S. PLATT and R. A. WEBB—

Clinical signs of dietary deficiencies. *Proc. Nutrit. Soc.*, 1944, **1**, 11.

Fermentation and human nutrition. *Ibid.*, 1946, **4**, 132.

R. A. WEBB—

The chemical micro-biology of Kaffir beer. (With demonstration). *Biochem. J.*, 1945, **39**, xlix P.

Research on Nutrition at the Lister Institute of Preventive Medicine, London

(i) *Medical Research Council staff*:—

S. S. Zilva, D.Sc., Ph.D., F.R.I.C.
G. A. Snow, M.Sc., Ph.D. (*till 1945*).
C. L. Arcus, B.Sc. Ph.D. (*till 1941*).
J. R. Penney, B.Sc., Ph.D. (*from 1941*).
H. A. Painter, B.Sc., A.R.I.C. (*from June, 1944*).

(ii) *Medical Research Council staff*:—

Miss E. Margaret Hume, M.A.

Attached worker:—

Miss Hannah Henderson Smith (*part-time*).

(i) Research on vitamin C by Dr. S. S. Zilva and his collaborators at the Lister Institute of Preventive Medicine—and, for part of the war period, at the East Malling Research Station, Kent—was divided between studies with immediate practical implications under war conditions, and fundamental investigations of the biochemistry of the vitamin.

Vitamin C in Army Rations

At the request of the War Office, work had been begun as long ago as 1937 on the content and stability of ascorbic acid (vitamin C) in canned foodstuffs, such as are used for field rations. By the outbreak of war

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sufficient preliminary information had been gained to concentrate attention on the possibilities (*a*) of increasing the ascorbic acid content of canned foodstuffs by the inclusion of suitable varieties of potatoes, lifted at the correct time, and (*b*) of finding articles in the field ration which could usefully be fortified by the addition of synthetic ascorbic acid. From the advisory aspect, an important task was to combat the prevailing but ill-founded opinion that a high intake of ascorbic acid was necessary for health.

As noted in the Annual Report for 1938-1939, it has been found, in a preliminary study, that the ascorbic acid content of the meat and vegetable ration could be increased by including certain varieties of potatoes, lifted early. Efforts, therefore, were made to discover whether this held true in large-scale production. Material from the base provision depots of Paiforce, and of the Middle East and West Africa Commands was examined, as well as rations stored in the United Kingdom. The amount of ascorbic acid in the canned potatoes was shown generally to be satisfactory, especially if the canning had been done soon after lifting, and it was found that no appreciable diminution of the ascorbic acid content occurred on storage even in hot climates. Thus ¼-½ lb. of canned potatoes, with their liquid, supplied about 15 mg. of ascorbic acid: such a daily dose, although below the League of Nations target value, is sufficient not only to prevent scurvy but to maintain apparent good health for considerable periods of time, provided that the diet is adequate in other respects.

Although potatoes are not one of the richest sources of ascorbic acid, the stability of the canned product makes it reliable in emergency. In contrast to this, preliminary experiments with dried cabbage and dried soup, prepared on behalf of the Ministry of Food, showed that the ascorbic acid in these preparations was not stable.

The suitability of jam and chocolate as media for enrichment with supplementary ascorbic acid was investigated. It was found that, with jam, the fall in vitamin content was very small both during preparation under factory conditions and on storage. However, jam is an inconvenient vehicle for the administration of extra vitamin C in the field. Chocolate, on the other hand, suffered a significant loss of the synthetic vitamin after 12 months' storage, although the losses in preparation, or due to the high temperatures of tropical climates, were small.

As a result of these experiments, it was reported to the Service authorities that although the large-scale enrichment of chocolate with ascorbic acid was not financially justifiable, this expedient might be useful on a limited scale in certain circumstances. It was, in fact, adopted, with full justification, during the Burma campaign.

The discoloration of ascorbic acid tablets on storage, and its significance with regard to the stability of the vitamin, were investigated. It was found that the combined effects of high humidity and high temperature caused deterioration of ascorbic acid, and led to the development of the colour—the binding material of the tablet being, in this, an important controlling factor. However, the commonly encountered discoloration was of no medical significance. A colour standard was devised to indicate any serious loss of potency.

Various special investigations, such as the examination of captured enemy rations, were undertaken at the request of the War Office.

Biochemical and Other Studies of Vitamin C

Work by Dr. Zilva and Dr. C. L. Arcus was continued on the anaerobic photolysis of ascorbic acid by ultra-violet light in the absence of sensitisers, in extension of a study begun with Dr. A. E. Kellie. Conclusive evidence

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was obtained that at least most of the ascorbic acid is degraded with the intermediate formation of dehydroascorbic acid. Owing, however, to the protection afforded to ascorbic acid by glutathione in the skin, it is improbable that this reaction occurs in the body.

Dr. Zilva and Dr. Kellie re-examined the significance of Harrison's finding that the increase in respiration which took place on the addition of ascorbic acid to surviving liver slices from guinea-pigs fed on a scorbutic diet, was greater than that noted on the addition of the acid to liver slices from animals fed normally; from similar experiments with liver tissue from animals which had received a diet quantitatively restricted, but containing ample vitamin C, they concluded that the difference observed was not connected with scurvy, but was associated with the supervening state of malnutrition in the animals fed on the scorbutic diet. With the co-operation of Dr. G. A. Snow, it was also demonstrated that similar changes could be produced by placing the liver slices in other reducing agents, themselves inactive against scurvy, but related chemically to *l*-ascorbic acid. These experiments led to an examination of the influence on the increased tissue respiration of a range of inhibitors known to modify carbohydrate catabolism.

Dr. Zilva investigated the influence of intermittent consumption of moderate doses of vitamin C on the development of scurvy in guinea-pigs. He found that amounts corresponding to multiples of the minimum daily dosage required to protect these animals from scurvy, were capable of preventing the disease when administered at relatively long intervals.

During a trial of the suitability of condensed milk as a vehicle for fortification with synthetic ascorbic acid, it was observed that there was a loss of antiscorbutic activity when the " fortified " milk was mixed with tea: this was due to the production of the oxidation product, dehydroascorbic acid. It appeared that this reaction was due to organic catalysts in the tannin fraction of the tea; the nature and properties of these and other catalysts in vegetable extracts and infusions have been intensively studied.

With a view to an investigation of the metabolism of 2:3-diketo-*l*-gulonic acid (a compound produced by the mutarotation of dehydro-*l*-ascorbic acid in acid solution), a method for the estimation of this substance in small quantities was devised by Dr. Zilva and Dr. J. R. Penney. Although the same reaction is given by other α-keto acids, it was found in practice that small quantities of added 2:3-diketo-*l*-gulonic acid could be determined with reasonable accuracy in blood, plasma, liver, kidney, muscle and urine by this means. Using the new method, Dr. Zilva and Dr. Penney carried out a detailed chemical investigation of the ring opening of dehydro-*l*-ascorbic acid, the first reversible oxidation product of *l*-ascorbic acid; parallel studies were then made *in vivo*, by introducing the primary oxidation products of *l*-ascorbic acid parenterally, and orally, into guinea-pigs and investigating what happened to them in the body. Whilst 2:3-diketo-*l*-gulonic acid was hardly absorbed when given orally, when introduced parenterally it distributed itself amongst the tissues, the greater part being subsequently excreted by the kidney during the first four hours. Dehydro-*l*-ascorbic acid, on the other hand, when taken orally, was gradually absorbed; it was then partly converted to 2:3-diketo-*l*-gulonic acid and partly reduced to *l*-ascorbic acid: these products filled the tissues of the " unsaturated " guinea-pigs, while a proportion was eliminated by the kidney. The chief deduction from these results was that if, in the metabolism of the animal organism, ascorbic acid is a link in a co-ordinated chain of reactions in which it is alternately oxidised to dehydro-*l*-ascorbic acid and reduced to its original form, some of the dehydro-*l*-ascorbic acid will probably be converted irreversibly to 2:3-diketo-*l*-gulonic acid. Accordingly, since the quantities of dehydro-*l*-ascorbic acid involved at any time in this

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reaction will be minute, the rate of permanent disappearance from the body of *l*-ascorbic acid will be extremely slow. This fact would explain the reason why a long time has to elapse, after deprivation of vitamin C, before scurvy develops, and also why the consumption of so little of the vitamin is required to prevent the onset of the disease.

The only specific method for the estimation of vitamin C is the biological method. Unfortunately the accuracy of this procedure is not high. The reducing capacity of unknown substances can, of course, be determined with great accuracy by using indophenol as an indicator, but the method is not specific for l-ascorbic acid. Nevertheless, when used critically in conjunction with biological tests it may serve to enhance the accuracy of the latter. Lugg has devised a procedure which is based on the fact that *l*-ascorbic acid and other indophenol-reducing substances combine with formalin at different rates according to the *p*H of the reacting solution, and thus lose their capacity for reducing the indicator. Dr. Zilva and Dr. Snow have submitted Lugg's method to a detailed examination by making a study of the kinetics of the combination of *l*-ascorbic acid and chemically related substances with formalin, as well as of the chemical character and structure of the formalin-*l*-ascorbic-acid complex. It was found that although Lugg's procedure greatly improves the specificity of the indophenol reducing capacity of unknown solutions, the specificity is not absolute and critical judgment is still necessary in interpreting the results. Apart from the fact that *l*-ascorbic acid cannot be distinguished by this method from its closely related, but biologically inactive, analogues and from other inactive reducing substances, every determination must be considered in relation to the circumstances of the particular case, in order to correct for the possible presence of interfering substances. These compounds may either be substances capable of reducing indophenol, or they may exert an influence on the rate of combination of *l*-ascorbic acid with formalin, thus vitiating the method. In sequence to this study, Dr. Zilva and Dr. Snow have worked out a convenient procedure based on Lugg's formalin method, and have introduced formulae to correct for the presence of certain interfering substances.

Another recent method of estimating vitamin C, namely that of Roe and Kuether, has been critically examined. In doing so, Dr. Zilva and Dr. Penney found that certain compounds produced by heating carbohydrates simulated the reaction of *l*-ascorbic acid: however, the rate of reaction of the primary oxidation products of these substances was more rapid than that of *l*-ascorbic acid, its analogues, or 2:3-diketo-*l*-gulonic acid. It was thus possible to work out conditions under which interference with the test could be entirely eliminated in a known mixture of any of these compounds and *l*-ascorbic acid, providing the analogues and 2:3-diketo-*l*-gulonic acid were absent. In an unknown solution, however, the error due to the presence of such interfering substances could only be reduced but not eliminated. A careful comparison of the results obtained by Lugg's method as modified by Dr. Zilva and Dr. Snow, and by the modified Roe and Kuether's method, yielded information concerning the limitations of each procedure. It was also found that, when the two methods were used in conjunction, more information could be obtained about the chemical character of interfering substances than by using either method alone: in this way, some interfering substances not previously observed were detected.

Hirst and his collaborators postulated that 2:3-diketo-*l*-gulonic acid is an intermediate product in the oxidative degradation of *l*-ascorbic acid: however, this compound had not hitherto been isolated, and, pending its

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isolation, several questions bearing on the part played by *l*-ascorbic acid in nutrition remained unsettled. Dr. Zilva and Dr. Penney succeeded in isolating the barium and calcium salts of this acid, and have thus been able to clarify, with some degree of finality, the behaviour of 2:3-diketo-*l*-gulonic acid in the animal body. It was shown that ring closure in 2:3-diketo-*l*-gulonic acid with the production of *l*-ascorbic acid does not take place *in vivo*, although this can be achieved *in vitro* by treatment with hydriodic acid. Furthermore, *l*-ascorbic acid produced *in vitro* from the isolated salt of 2:3-diketo-*l*-gulonic acid was found to be chemically and biologically identical with authentic *l*-ascorbic acid. Calcium diketo-gulonate produced, on reduction with hydrogen sulphide, an indophenol-reducing substance which was biologically inactive. Further support is thus given to the view that, if any reduction of 2:3-diketo-*l*-gulonic acid takes place in the animal body, it does not lead to the formation of *l*-ascorbic acid.

In a long series of experiments, Dr. Zilva, in collaboration with Dr. C. West of the Ditton Laboratory of the Department of Scientific and Industrial Research, at East Malling, has been able to demonstrate that Bramley's Seedling apples can synthesise ascorbic acid during storage at 3° C. The evidence strongly suggests that, in the young apples, the vitamin is formed from a chemically related precursor present in the fruit.

C. L. Arcus and S. S. Zilva—
The photochemical decomposition of *l*-ascorbic acid. II. *Biochem. J.*, 1940, **34**, 61.

J. R. Penney and S. S. Zilva—
The determination of 2:3-diketo-*l*-gulonic acid. *Biochem. J.*, 1943, **37**, 39.
The chemical behaviour of dehydro-*l*-ascorbic acid *in vitro* and *in vivo*. *Ibid.*, 1943, **37**, 403.
The isolation of barium and calcium diketo-*l*-gulonates and the biological significance of 2:3-diketo-*l*-gulonic acid. *Ibid.*, 1945, **39**, 1.
Interfering substances in the Roe and Kuether method for the determination of ascorbic acid. *Ibid.*, 1945, **39**, 392.

A. E. Kellie and S. S. Zilva—
The action of *l*-ascorbic acid on the *in vitro* respiration of liver tissue from guinea-pigs on a restricted diet. I. *Biochem. J.*, 1941, **35**, 783.

G. A. Snow and S. S. Zilva—
The action of *l*-ascorbic acid on the *in vitro* respiration of liver tissue from guinea-pigs on a restricted diet. II. *Biochem. J.*, 1941, **35**, 787.
The catalytic oxidation of ascorbic acid in the presence of tea infusions. *Ibid.*, 1942, **36**, 641.
A critical examination of Lugg's method for the determination of *l*-ascorbic acid. *Ibid.*, 1943, **37**, 630.
A critical examination of Lugg's method for the determination of *l*-ascorbic acid. II. *Ibid.*, 1944, **38**, 458.

C. West and S. S. Zilva—
Synthesis of vitamin C in stored apples. *Biochem. J.*, 1944, **38**, 105.

S. S. Zilva—
Vitamin C in collective feeding. *J. Roy. Nav. Med. Serv.*, 1941, **27**, p. 64.
The influence of intermittent consumption of vitamin C on the development of scurvy. *Biochem. J.*, 1941, **35**, 1240.
An evaluation of the vitamin-C position. *Brit. med. Bull.*, 1944, **2**, 217.

(ii) Miss E. M. Hume had the half-time assistance of Miss H. Henderson Smith throughout the war. In September, 1939, their work was transferred from the Lister Institute to Cambridge, where they hal the hospitality of Sir Charles Martin until the beginning of 1946.

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Work on behalf of the Accessory Food Factors Committee

As Secretary of the Vitamin A and Vitamin E Sub-committees of the Accessory Food Factors Committee, Miss Hume took a large part in the organisation of a number of collaborative researches which have been described on pp. 105-113. Among these were the work on the standardisation of vitamin A, its assay in wartime margarine, and the experiments carried out at Sheffield to establish the human requirement of the vitamin. Miss Hume, assisted by Miss A. M. Copping, also organised the biological tests undertaken in many laboratories in different countries to establish a standard for vitamin E. She, further, had an important share, as already indicated on p. 106, in compiling the data on the vitamin content of various foods which were later incorporated in *Medical Research Council War Memorandum* No. 14.

Vitamin A Value of Bread and Potatoes

Bread and potatoes contain a very small amount of carotene; nevertheless, they comprise such a large part of the human dietary that their contribution as a source of vitamin A merited study. Miss Hume found that rats fed on a diet composed almost wholly of potatoes, without other source of carotene or vitamin A, could live indefinitely in very fair health, showing that the carotene content of potatoes is not so small as to be negligible. "Wholemeal" (92 per cent. extraction) and "white flour" (72 per cent. extraction) were prepared from the same grist, and one part of the white flour was bleached by a process involving the use of ultra-violet light. Rats, maintained on diets composed almost entirely of one of the flours and with no added source of vitamin A, survived an average time of 80 days with the wholemeal and unbleached white flour diets, but died after an average period of about 55 days when receiving the bleached white flour. There is thus a small amount of biologically active carotenoid distributed throughout the wheat grain, and destroyed by bleaching with ultra-violet light, but it is scarcely sufficient to be of practical importance.

The Dunn Nutritional Laboratory, Cambridge

Staff:—

L. J. Harris, Sc.D., D.Sc., Ph.D., F.R.I.C. (*Director*).
T. Moore, D.Sc., Ph.D.
Miss E. M. Cruickshank, Ph.D
E. Kodicek, M.D., Ph.D.

Attached workers:—

L. W. Mapson, Ph.D. (*seconded from Food Investigation Board*).
V. H. Booth, Ph.D. (*member of scientific staff, Agricultural Research Council*).
Y. L. Wang, Ph.D., B.Sc. (*till 1944*).
Miss K. Sgalitzer (Mrs. Osancova), B.A. (*Research grant from Imperial Bureau of Plant Breeding and Genetics; 1941-1944*).
Mrs. R. Morgensternova, B.Sc. (*Research grant from Imperial Bureau of Plant Breeding and Genetics; since 1945*).
Mrs. J. F. Mackworth, M.A. (*1944-1945*).

Visiting workers for more than short periods:—

J. Yudkin, M.D., Ph.D. (*Halley Stewart Fellow; till 1943*).
G. G. Banerji, B.Sc. (*till 1940*).
Miss S. Highman, M.Sc. (*since 1944*).
G. W. Robertson, Ph.D. (*1940-1941*).
J. Tosic, Ph.D., M.Sc. (*1943-1944*).

The research programme of the Laboratory during the war years can be grouped under the following headings:—(1) the examination of wartime foods

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and dietaries, including Service rations, (2) tests on populations for nutritional status and human requirements of nutrients, (3) the development of methods for estimating vitamins, and (4) studies in nutritional physiology.

Nutritional Value of Wartime Foods and Dietaries

Army rations.—As already indicated on p. 100, work on the vitamin content of Service rations had been in progress at the Laboratory well before the war. Dr. Harris and his colleagues found that the Army emergency ration, which for military reasons had to be packed in tins, and thus subjected to heat treatment, was in consequence deficient in the anti-beriberi vitamin (B_1). A wheatmeal biscuit, in which the vitamin B_1 was found to have been destroyed by the baking powder used in its manufacture, was ineffective in replacing the deficiency, and a commercial yeast extract, suggested as a compensating source of the vitamin, was shown to lose much of its potency on storage. The remedy eventually worked out was to substitute the less alkaline ammonium carbonate for the sodium bicarbonate in the baking powder, or, better, to bake the biscuits with yeast instead of baking powder. In the course of this investigation large numbers of assays were carried out, including tests of the biscuits after storage under adverse conditions in the tropics. It was also shown that a further substantial improvement in the vitamin B_1 content of the biscuits could be brought about by substituting wholemeal flour for the less highly extracted wheatmeal flour.

Similarly, certain other Service dietaries, including particularly the standard Naval ration for use afloat, were examined and suggestions made for their improvement.

Dehydrated foods.—In the war of 1914-18 the use of dried vegetables had resulted in outbreaks of scurvy, as the method of drying caused an almost complete destruction of vitamin C. It seemed likely, however, that if this difficulty could be overcome, dehydrated vegetables would prove a valuable component of Service dietaries, for use in special circumstances. In conjunction with the Low Temperature Research Station of the Food Investigation Board, Department of Scientific and Industrial Research, an investigation was therefore undertaken to achieve this end.

To summarise the final outcome of an extended enquiry, it was found that the conditions which had to be observed to secure maximum preservation of vitamin C and other nutrients in the dried vegetables were as follows. The raw product had first to be subjected to a preliminary "scalding" or "blanching" process, in the presence of sulphite, preferably the same scalding liquor being used repeatedly, so as to prevent undue washing away of nutrients (this is the so-called "serial scald"). The subsequent drying operation must then be carried out at a dry bulb temperature of less than 65° C. For successful storage, the product must be packed in tins in an inert gas, nitrogen or carbon dioxide, and it is necessary that the relative humidity of the gas should be low, after equilibrium has been attained in the sealed tin.

Cabbages, potatoes, carrots, beans, swedes, cauliflowers and other vegetables were all successfully dehydrated by such means, and were used on a considerable scale during the war. The processed food after reconstitution and cooking was found to compare favourably, in its antiscurvy potency, with fresh cooked vegetables.

These investigations on dehydrated foods were later extended to include other foodstuffs besides vegetables, and to secure the conservation of other vitamins as well as vitamin C. Carotene (provitamin A), *e.g.*, in carrots, was found to be little affected by dehydration, nor was its degree of biological availability, as tested on rats, measurably affected. In dried eggs, dried

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meat, dried milk and other products manufactured by the new approved procedures, there was relatively little destruction of various vitamins of the B_2 group, including nicotinic acid and riboflavin; the loss of vitamin B_1 might be considerable, but it could be reduced, in the case of meat, by an increase in acidity during the early stages of preparation.

Meat dried at temperatures up to 80° C. was found to have its digestibility and biological value unimpaired: with high temperature drying, however, for example at 125° C., the protein of the meat was found to be some 30 per cent. inferior to fresh meat in its growth-promoting activity, as judged by tests on rats. Dried protein from grass, the use of which had been advocated for human food during the war, was shown to be deficient in an essential amino-acid, methionine. In growth-promoting activity, grass protein was not so good as the protein of lucerne, and both were inferior to milk protein.

In these investigations, Dr. L. W. Mapson was mainly responsible for the tests on vitamin C, Dr. E. Kodicek for those on the B group of vitamins, and Dr. E. M. Cruickshank for those on carotene and vitamin A, and for the tests on dried egg and the biological assays.

Loss of nutrients in cooking.—As fresh fruits and vegetables were in short supply during the war, and especially in the winter months, tests were made by Dr. Mapson and others to ascertain those conditions during cooking, both in the household and on a large scale, which would cause the least destruction of vitamin C. It was found that the loss of vitamin C was lessened if attention were paid to the following rules. The vegetable should be coarsely cut into strips and not too finely shredded; it should be cooked in the minimum possible quantity of water (in order to avoid an undue amount of the vitamin being dissolved out); the water should be brought rapidly to the boil; the time of cooking should be kept short; and, lastly, the cooked dish should not be kept hot longer than necessary before serving. The most serious losses were due to vitamin C dissolving into the cooking water, and to its destruction during standing on the " hot plate ". These findings were communicated to the Ministry of Food, and were accorded wide publicity among housewives and caterers.

In another investigation, Dr. Mapson showed that bicarbonate of soda could be used in the cooking of highly acid fruits (thus saving sugar) without serious effect on their vitamin C content; with vegetables, however, an increased rate of deterioration occurred after cooking, during the time the vegetables were kept hot before consumption. When meat was cooked by roasting, there was a considerable loss of vitamin B_1 and relatively small losses of riboflavin and nicotinic acid, according to tests carried out by Dr. Cruickshank, Dr. E. Kodicek and Dr. Y. L. Wang.

Analysis of fortified products, special food preparations, etc.—Fortified products such as vitaminised margarine (containing vitamins A and D), fruit juice, fish-liver oils and vitamin tablets, for the use of expectant mothers and babies, and vitaminised chocolate, were examined to ascertain the appropriate conditions for safeguarding the activity and stability of their vitamins. In addition, a considerable number of common foodstuffs were analysed for vitamin content, in order to supply the Ministry of Food and Ministry of Health with figures for comprehensive tables on the nutritive values of wartime foods (see also p. 106). Many other special preparations were similarly tested for various Government Departments. In a collaborative test, tinned herrings were examined for the Ministry of Food, and found to be a disappointing source of vitamins A and D, compared with fresh herrings. Tinned salmon was found to be poor in vitamin A; sheep liver was shown to be considerably richer than ox liver in its vitamin A content, and the latter, in turn, to be richer than either calf or pig liver. Wheat which had been subjected to

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fumigation to destroy insect pests was examined for the Pest Infestation Laboratory, Department of Scientific and Industrial Research, to determine the effect on its vitamin content, and vitamin capsules used by the Ministry of Health for climinal trials were similarly assayed to ascertain their biological potency. Some new types of highly potent yeast, examined in collaboration with Dr. A. C. Thaysen (p. 112) of the Department of Scientific and Industrial Research, were found to be extremely rich in vitamin B_1, sometimes containing as much as ten times the normal amount; their content of other B vitamins was not, however, exceptionally high. When bread was fortified with these potent yeasts, or with crystalline vitamin B_1, it was shown that there was relatively little loss of activity in the baked product. *Creta praeparata,* if added in the amounts used in the National loaf, had little adverse effect on vitamin B_1 content of the bread, or on the absorption of phosphate by the animal organism.

A comprehensive study of the vitamin B_1 content of potatoes as influenced by seasonal and varietal differences was carried out by Dr. Wang, on behalf of the Ministry of Health: definite differences between varieties, but no seasonal fluctuations, were observed. Other studies on potatoes are described on p. 297, below.

Communal feeding.—Parallel with this work on wartime foods, and as a check on the actual intakes of the community, surveys were made of the nutritional adequacy of meals as served, for example, at British Restaurants, works canteens, army camps, local schools and at a residential institution. Those taking part in these surveys included Dr. G. N. Jenkins, Miss M. Olliver, Dr. G. V. James and Dr. Harris. In the course of the surveys, a critical study was made of the various methods used for the estimation of protein, fat, carbohydrate, vitamin B_1 and vitamin C, to determine which were the most reliable.

Seasonal intake of vitamin C.—At a residential home for boys, Miss Olliver and Dr. Harris recorded the intake of vitamin C, day by day, for over five years during the war. The same characteristic seasonal curve was seen each year, the daily intake of vitamin C rising to a maximum about August to September and then dropping again, the lowest ebb occurring about March to April. The most important sources of vitamin C throughout the year were green vegetables and potatoes.

Tests for Nutritional Status

Vitamin C " saturation " test.—Dr. Harris has shown that by giving standard test doses of vitamin C daily and counting the number of days until a condition of " saturation " is brought about (as marked by an immensely increased output of the vitamin in the urine), an individual's vitamin C " status " can be quantitatively assessed. Control tests were done at intervals over a period of five years on groups of boys kept on various known graded intakes of vitamin C. The results confirmed that the number of days taken to saturate was inversely related to the past level of intake, and that with a daily intake of 50-75 mg. of ascorbic acid (the high allowance recommended by some American authorities) saturation is already reached on the first day of dosing, with 30 mg. (the League of Nations standard of requirement) by the first to second day, and so on in proportion with each smaller daily intake; conversely, a man who takes 7-10 days to " saturate " has low vitamin C reserves and may develop scurvy. A detailed critical study of this technique was published and the general conclusion was that the test is reliable.

" Saturation " and " tolerance " tests for vitamin B_1.—Two methods were devised by Dr. Harris for assessing the nutritional status of human subjects

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with regard to vitamin B_1. The first is a saturation test similar to that just described for vitamin C, and the second, which has since been widely used in the U.S.A. and elsewhere, consists of a carbohydrate-tolerance test; the latter depends on the excretion in the urine of abnormal " bisulphite-binding substances ", mostly pyruvic acid, when there is a deficiency of vitamin B_1.

Test for nicotinic acid.—The test, described by Dr. Harris and Dr. W. D. Raymond, for assessing the nutritional status with regard to nicotinic acid (the so-called " anti-pellagra vitamin ") depends on a chemical analysis of urine, both before and after test dosing, using the reagent *p*-aminoacetophenone for measuring the excretion of nicotinic acid. The use of this reagent was developed in various ways by Dr. E. Kodicek and Dr. Wang. It was found that the quantitative estimation of certain methylated derivatives of nicotinic acid proved the best indication of nicotinic acid reserves. A number of pellagrins were shown to excrete little or none of these substances in the urine.

Vitamin A reserves in man.—Dr. Moore continued the work, which he had begun some years before the war, of estimating the average reserves of vitamin A in different classes of human subjects in England, as judged by chemical analyses on *post mortem* specimens of liver. Critical studies of the dark-adaptation method of assessing vitamin A deficiency were carried out by Dr. Harris and Dr. M. A. Abbasy; it was concluded that the principle of the method was reliable, but that in practice numerous precautions were necessary to prevent misinterpretation of results. Parallel studies of this method were made by Dr. J. Yudkin and Dr. G. W. Robertson in conjunction with several other workers; such factors as variation between individuals, and the effect of age, being specially examined. Dr. Yudkin, in conjunction with an ophthalmologist, Dr. J. H. Kodicek, also published an account of the use of the slit-lamp microscope in nutrition surveys. It was considered that examination of the epithelial layer of the eye was more likely to be useful than examination of the sub-epithelial tissues as recommended by Kruse in America.

Trials of vitamin supplements, and other nutritional surveys.—In several elementary schools in Cambridge, about 1,000 children between the ages of 4 and 11 years were under examination by Dr. Yudkin, in collaboration with Mrs. M. Russell Davis, Mr. E. B. Grandison and Dr. Jenkins, in a controlled vitamin-feeding test with vitamins A, B_1, C and D. After a year's dosing with the vitamin supplements, no difference could be detected between the " vitamin " children and controls who had received no supplements, as measured by the following criteria:—increase in height or weight, haemoglobin level, strength of grip, intelligence, educational attainment, dark adaptation, resting pulse rate, vital capacity, breath holding, or endurance test, though there was some diminution, apparently statistically significant, in the incidence and duration of colds in the " vitamin " children. It was observed, in this study that children from large families, or from a poor part of the town, were on the average shorter and weighed less, and had lower haemoglobin levels and weaker grip, than the children from smaller families or from a better part of the town, the inference being that lack of some dietary constituents other than the vitamins given in the test was responsible for the observed differences in nutritional status. Similar conditions were found in a survey of mothers and children from working-class families in industrial towns in Scotland, the nutritional status of both mothers and children being closely correlated with the amount of money available for food; for example, in families where this was more than 7s. 2d. per head weekly, the children were on the average 1¼ inches taller, 6 lb. heavier and had 3 per cent. more haemoglobin, than those in families where it was less than 7s. 2d.

In a survey of factory workers in Birmingham, Dr. Yudkin and Dr. Robertson noted an appreciable gain in body weight of comparable groups

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of workers during the years 1941-42 and 1942-43: estimations of haemoglobin levels, however, did not reveal any marked changes during the period of observation.

Dr. Moore and Dr. Mapson were both actively concerned in the experiments conducted under the auspices of the Accessory Food Factors Committee (p. 419) into the human requirements of vitamins A and C. This work was carried out at the Sorby Research Institute, Sheffield, and has been described on pp. 108-110 above. Dr. Moore, in addition to carrying out many routine vitamin estimations, was a member of the Sub-Committee which directed the vitamin A experiment, while Dr. Mapson was correspondingly engaged in the vitamin C experiment.

Assay and Standardisation of Vitamins

Vitamin C.—Dr. Harris and Miss Olliver published a comprehensive study of the reliability of the chemical method for estimating vitamin C in foodstuffs, by rapid titration against Tillmans' dye. It was concluded that for all ordinary raw, cooked or processed fruits and vegetables this method gives accurate results. In certain instances, however, "interfering substances" have been found to invalidate the results obtained: further chemical methods of estimation were therefore devised. For determining vitamin C in coloured extracts, when the usual titrimetric method is unsuitable, Dr. Harris, Dr. Mapson and Dr. Wang developed a potentiometric method, depending on the use of a novel type of electrode. Dr. Mapson described convenient procedures for estimating vitamin C in foodstuffs to which sulphur-dioxide has been added as a preservative. Dr. Kodicek showed how the polarograph (dropping mercury electrode) might also be used for estimating vitamin C, and applied the method, in collaboration with Dr. Mapson, to the analysis of numerous fruits and vegetables.

Vitamin B_1.—An extensive study of the possible sources of error in the chemical estimation of vitamin B_1 by the "thiochrome" test was carried out by Dr. Harris and Dr. Wang. Chemical and biological assays were found generally to agree within an error of less than 15 per cent. As part of the collaborative research organised by the Vitamin B Sub-Committee, a special modification of the thiochrome test was devised for the estimation of vitamin B_1 in National Wheatmeal flour (see p. 106). Also on behalf of the Vitamin B Sub-Committee, Dr. Harris, Dr. Moore and Dr. Wang made a systematic examination of the various methods (titrimetric, biological and spectrographic) for testing the purity of preparations of aneurin hydrochloride, giving special attention to the specimen to be used as the new subsidiary standard. Methods were also worked out on behalf of the British Pharmacopoeia Commission for assessing the purity of specimens of aneurin (p. 111).

Riboflavin.—Dr. Kodicek and Dr. Wang elaborated an improved procedure depending on fluorimetry for the estimation of riboflavin: the results agreed well with those obtained by microbiological assay. By using a new medium for the cultivation of the micro-organism in the latter method, a three-fold increase was obtained in the sensitivity of the determination. Dr. Kodicek and his colleagues observed that the naturally occurring *cis*-forms of unsaturated fatty acids interfere in the microbiological assay of riboflavin, and must therefore first be removed. For the determination of riboflavin in concentrates or foodstuffs rich in it, such as liver or vitamin capsules, Dr. Kodicek found that a polarographic method could be employed.

Nicotinic acid.—Dr. Kodicek published the details of a method for determining nicotinic acid in foodstuffs and animal tissues. Using this method, it was shown that egg-white differed from most other protein foods in being

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deficient in nicotinic acid; cows' milk was also unexpectedly poor in this respect, but coffee was remarkably rich. All these findings were confirmed by biological tests on puppies. Another finding by Dr. Kodicek was that in cereals a "chromogen" or precursor of nicotinic acid is present. Dr. Kodicek and Mrs. Mackworth made progress towards its separation.

Carotene and vitamin A.—Having found that current methods of estimating carotene in vegetable tissues generally gave too low results, Dr. V. Booth worked out an improved technique. A simple method for estimating total carotenoids was also devised.

Dr. Cruickshank and Dr. Kodicek examined the problem of estimating vitamin A in the presence of xanthopylls, *e.g.* in dried eggs, and a re-examination of the methods for biological standardisation of vitamin A was begun by Dr. Moore.

Vitamin E.—Dr. Moore and Dr. J. Tosic reinvestigated the chemical test for vitamin E with α-ά-di-pyridyl, aud succeeded in making it more specific and accurate. Dr. Moore and Dr. K. R. Rajagopal developed spectroscopic methods for the determination of the distribution of vitamin E in animal tissues.

Studies in Vegetable Breeding

As part of a long-term research, workers at the Laboratory began an investigation into the influence of genetic factors on the content of vitamins and other nutrients in certain vegetables.

During work on carrots, sponsored jointly by the Agricultural Research Council and the Medical Research Council, Dr. Booth examined many varieties for their carotene content; this averaged 12 mg. per 100 g. of fresh, mature carrot. Factors influencing the carotene content, apart from genetic variation, were found to include the dates of sowing and harvesting, and the conditions during growth. A "biopsy" technique was developed for the sampling of carrots while still growing, and this was used to assess the results of selective breeding: the prospects of raising the carotene content appear to be good.

A parallel investigation on potatoes, jointly sponsored by the Imperial Bureau of Plant Breeding and Genetics and the Council, was undertaken by Miss Sgalitzer (Mrs. Osancova). A systematic comparison has been begun of the nutritive properties of different varieties, including many wild potatoes from Central and Southern America, the majority of the specimens being provided by the Empire Potato Collection. It was found that much more vitamin C was present in some of the primitive potatoes than in ordinary domestic varieties. Breeding trials have accordingly been started.

Studies in Nutritional Physiology

Wound healing.—The effect of partial deficiency of vitamin C on the healing of bone injuries in guinea-pigs was examined by Dr. Kodicek with Dr. P. D. F. Murray, Reader in Biology at the University of London. A remarkable degree of hyperostosis was observed, associated with delay in healing, degeneration of muscle fibres and ankylosis of the joints.

Dr. Kodicek, working in collaboration with Dr. Honor B. Fell, of the Strangeways Research Laboratory (p. 371), and Dr. J. F. Danielli, of the Cambridge University School of Biochemistry, also studied the influence of acute and partial deficiencies of vitamin C on the production of the enzyme phosphatase in wounds of the skin. Phosphatase activity was found to diminish in proportion to the degree of deprivation of vitamin C, and the differentiation of collagenous tissue was adversely affected also. A connection between phosphatase secretion and the formation of collagen seems probable.

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Dr. Kodicek with Dr. Murray, and Dr. A. Stock of St. Bartholomew's Hospital Medical School, studied the distribution of phosphatase in ectopic bone which had developed in animals as a result of the transplantation of bladder tissue.

Contrary to the conclusions of Ecker in America, but in agreement with the results of Dr. S. S. Zilva in this country, Dr. Kodicek, and Dr. B. Traub of the Department of Pathology at Cambridge, found that the complement titre of the blood of guinea-pigs was not affected by various degrees of deficiency of vitamin C.

Vitamin C and enzyme systems.—Vitamin C is known to inhibit certain enzyme systems, and Dr. Mapson made a study of the underlying mechanism. With urease and β-amylase, he found that this inhibition was effective only in the presence of copper ions. The ascorbic acid inhibited only in so far as it was able to reduce copper from the cupric to the cuprous state. Vitamin C in its reversibly oxidised form, dehydro-ascorbic acid, had no inhibitory influence, but certain dienol derivatives, bearing some structural resemblance to ascorbic acid, namely reductone, reductic acid and dihydroxymaleic acid, all inhibited these enzymes in the presence of copper.

Vitamin C in relation to oxidants and antoxidants.—Oxidation of vitamin C was shown to be brought about in three ways: by the catalytic action of copper, by oxidants in the tissues, and by atmospheric oxygen. In control tests on pure ascorbic acid Dr. Mapson showed that salts of halides if present in sufficient amounts retarded oxidation; in smaller amounts they accelerated it. The action was found to be inter-related with the effect of copper and was antagonised by hydroxy-acids. Many of the observed effects could be explained by the influence of the halide ion on the alternate oxidation and reduction of the copper salts.

Biosynthesis of vitamins in plants and animals.—An investigation to ascertain the factors influencing the amounts of vitamin C and provitamin A (carotene) synthesised by plant tissues was undertaken by Dr. Cruickshank and Dr. Mapson, cress seedlings being the test organism. It was found that the amount of utilisable base was a principal factor in determining the amount of vitamin synthesised. From her experiments on guinea-pigs Miss Cruickshank was unable to confirm the suggestion that, in mammals, injections of manganese favour the synthesis of vitamin C.

Fat and protein as sparers of vitamin B_1.—Work completed during the war indicated the importance of the fat and protein of the diet in reducing the body's requirements for vitamin B_1. With Dr. Harris, Mr. G. G. Banerji showed that among the other disorders in vitamin-B_1 deficiency which were alleviated by the addition of fat to the diet was the excretion of the abnormal products of metabolism, " bisulphite-binding substances ". Protein had the same effect. In continuation of these studies, Mr. Banerji and Dr. Yudkin showed that, although the extra fat or protein protected animals against this and other sequels of deficiency, they did not correct the latent error in metabolism as measured *in vitro* by the so-called " catatorulin " effect. The importance of this finding is that it indicates that the fat and protein of the diet, although largely converted in the body to carbohydrate, must then be metabolised along a different pathway from that of dietary carbohydrates.

Biochemical adaptation.—Dr. Yudkin found that whether rats were given moderate or high intakes of vitamin B_1 over long periods, after deprivation there was no difference in the rate of appearance of deficiency symptoms or in their severity. Acquired tolerance to alcohol was also studied in the rat: no difference was found between the " normal " and the " adapted " rat in the rate of oxidation of alcohol by the tissues or in the inhibitory action of alcohol on the oxidation of certain other substances.

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Effects of excess of vitamin A.—The toxic effect on rats of overdoses of vitamin A, given as the highly purified crystalline acetate, was studied by Dr. Moore and Dr. Wang. In young rats, skeletal fractures were the most characteristic lesion present; haemorrhages also were found. Dr. Moore and Mr. K. Rodahl observed that the livers of the polar bear and of the seal, *Phoca barbata,* were toxic, due to their high vitamin A content.

Vitamin A and the new-born.—The importance of colostrum for the health of new-born calves was re-emphasised by an investigation by Dr. Moore and Mr. A. W. Davies, with Mr. F. Blakemore and Mr. A. N. Worden, of the Institute of Animal Pathology. As suckling began, the vitamin A in the calves' blood rose towards the adult level: simultaneously, globulins appeared in the blood and reactivity towards antigens (such as those of *Brucella abortus*) developed, confirming the earlier work of Howe, Little and Orcutt. Vitamin A was more readily absorbed from colostrum than from oily media such as fish liver oil.

Excretion of vitamin A.—Dr. Moore and Dr. Rajagopal, working in collaboration with Dr. N. R. Lawrie, confirmed that, while in dogs vitamin A is normally excreted in the urine, in humans this occurs only in certain diseased states.

Interaction of vitamins A and E.—Dr. Moore, with Mr. Davies, found that, in rats, there is a relationship between the needs for vitamins A and E. In rats restricted to diets deficient in both vitamins the reserves of vitamin A were used up much more rapidly than in control animals given pure vitamin E as dl-α-tocopheryl acetate. A prolonged deficiency of vitamin E brought about a secondary deficiency of vitamin A, as indicated by the disappearance of this vitamin from the liver. The biological rôle of vitamin E in sparing vitamin A is probably similar to that observed *in vitro,* in which it acts as an antoxidant.

Abnormalities caused by deficiency of vitamin E.—A lesion which Dr. Moore found to occur in rats suffering from deficiency of either vitamin A or vitamin E was a whitening of their incisor teeth. This had previously been thought to be characteristic of vitamin A deficiency only, but Dr. Moore showed that it could be cured by the restoration of whichever of the two vitamins was missing. Dr. Moore also found that, in rats suffering from deficiency of vitamin E, the uterus and certain other tissues became stained a distinctive brown colour. With Dr. Wang, he showed that these tissues exhibited a characteristic fluorescence when exposed to ultra-violet light, and that the fluorescence provided a very delicate test for deficiency of the vitamin. No comparable fluorescence, however, could be detected in a number of human uteri examined. Human hearts showing " brown atrophy " were also examined, *post mortem,* and in some instances a certain degree of brown fluorescence was detected. Further work will be needed if these observations are to be related to clinical medicine.

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Bacterial Chemistry and Cell Metabolism

(i) The Bacterial Chemistry Research Unit, Lister Institute of Preventive Medicine, London

Staff:—

Sir Paul Fildes, O.B.E., M.B., F.R.S. (*Director*).
G. P. Gladstone, M. B.
G. M. Hills, B.Sc.
H. N. Rydon, D.Sc., Ph.D.
D. D. Woods, Ph.D.

Attached worker:—

D. Herbert, Ph.D.

(ii) The Cell Metabolism Research Unit, Sheffield

Staff:—

Professor H. A. Krebs, M.D., F.R.S. (*Director, part-time*).
H. McIlwain, Ph.D., D.Sc. (*since April, 1945; previously a Leverhulme Research Fellow*).

Attached workers:—

R. E. Davies, M.Sc.
Miss M. Danniell, B.Sc.

From 1934 till the beginning of hostilities the Council's Unit for Research in Bacterial Chemistry, directed by Dr. P. G. (now Sir Paul) Fildes, had been accommodated at the Middlesex Hospital, London. In 1940, in view of intelligence reports of German preparations for bacteriological warfare, the Council were asked by the Government to lend the services of members of their staff for active research into the possibilities of this development. The Bacterial Chemistry Research Unit was selected to be the nucleus of this organisation, under its Director, who was responsible to a War Cabinet Committee and later to an Inter-Services Committee. The work was located at a Ministry of Supply Experimental Station. Accordingly, in September 1940, Dr. Fildes, Dr. Gladstone, Dr. Woods and, later, Mr. Hills, left London to undertake the special duties, and subsequently Dr. Herbert and Lord Stamp joined them.

During this work much of medical interest emerged. The subject was treated from the academic point of view as a research into exploiting the pathogenic potentialities of bacteria and, conversely, into methods of protection against these. Considerable advance was made in knowledge of the conditions which favour bacterial attack, and of the mechanism of air-borne infections. The methods for assessing chemical clouds were adapted to bacterial clouds, and there is little doubt that these techniques will be of service in future medical studies. The production of pathogens in bulk was another requirement leading to the elaboration of new routines, which will certainly become established in medical work for providing sufficient quantities of bacteria for enzyme and antigenic analysis, and for the production of immunising substances. These methods have already been applied to immunisation against anthrax: an antigen has been prepared which has the advantage over existing vaccines in being free from bacteria and capable of producing massive immunity. Practical trials are planned.

In 1941 the remaining member of the original unit, Dr. H. McIlwain, a Leverhulme Research Fellow, went to Sheffield University, where he continued to work on problems of cell metabolism in the Department of Professor H. A. Krebs. At the end of the war Sir Paul Fildes returned to London, and the Bacterial Chemistry Research Unit was reorganised at the Lister Institute of Preventive Medicine. Meanwhile, in 1945, the Council had established a new unit at Sheffield, under the part-time direction of Professor Krebs, for research on cell metabolism.

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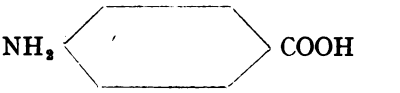
Mode of Action of Chemotherapeutic Substances

As a result largely of studies by Dr. Fildes and his associates it had been shown that the essential amino acid requirements of certain pathogenic bacteria were conditioned by their inability to synthesise these acids; the latter, which were known as " growth factors " for the bacteria concerned, had to be supplied in nutrient media. The view was taken that in the synthesis of new bacterial substance from simpler compounds a series of reactions occurred, brought about by enzyme action, each stage being marked by the formation of an " essential metabolite ". The first proof of the production of an essential metabolite in the course of synthesis of a higher compound was the demonstration by Dr. Fildes that indole was synthesised by many bacteria tested, and was used further by these in the synthesis of tryptophan. Other bacteria, which were shown to be incapable of this synthesis, required the supply of indole as a growth factor. A growth factor was therefore an essential metabolite which the particular bacterium could not itself synthesise. Clearly, interference with the production of an essential metabolite, whether growth factor or not, would inhibit bacterial growth. It was considered that the essential metabolites then known in bacteriology, or at least many of them, were common to all or most types of cell, and there was evidence to suggest that they would prove to be identical with animal vitamins.

Studies by Fildes, in 1939, of the antibacterial action of mercury showed that the metal combined *in vitro* with the sulphydryl group (a known bacterial essential metabolite) and that the resultant compound was not itself inhibitory to bacteria, provided there were no excess of mercury. It therefore seemed probable that the inhibitory action of the metal was due to the diffusible mercury salt entering the bacteria and rendering the sulphydryl group unusable. Further support to this hypothesis was given by the fact that the addition of excess sulphydryl group overcame the inhibitory action of the mercury. With the introduction of the sulphonamide drugs it became a question whether the mechanism of their inhibitory effect was similar to that postulated for mercury. Prolonged experiments were carried out to test whether any known essential metabolite could be associated with the action of sulphanilamide, but without success. In 1939, however, Stamp showed that it was possible to reverse the action of sulphanilamide by an extract obtained from streptococci. It was assumed, therefore, that this extract contained an essential metabolite which was not one of the growth factors for streptococci, since all these were known. For convenience in extracting, Dr. Woods fractionated yeast extracts, and, in 1940, he obtained a material with well-defined chemical characters, which reversed the action of sulphanilamide. This material could not, for quantitative reasons, combine with sulphanilamide on a molecular basis as does the sulphydryl group with mercury, but it might act by competing for an enzyme of which it was the natural substrate. In this case it should follow that the substance in the extract had some structural resemblance to sulphanilamide; the substance was eventually identified as *p*-aminobenzoic acid.

Sulphanilamide



p-aminobenzoic acid

This was clearly a discovery of major importance: it indicated that competitive inhibitors might be designed to block the metabolism of any essential metabolite. It was only necessary so to modify the structure of an essential

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metabolite that it could no longer function as such, while still retaining its power to use its original enzyme. In this way a rational basis was established for the synthesis of new chemotherapeutic agents.

It was not given to the Unit to support their hypothesis by demonstrating the correctness of the prediction that *p*-aminobenzoic acid was a hitherto unknown essential metabolite and an animal vitamin, because, with the exception of Dr. McIlwain, the members were occupied with other work during the war years. However, Rubbo and Gillespie (1940) in Australia proved the first prediction to be correct and Ansbacher (1941) the second. In America the concepts of Dr. Woods and Dr. Fildes have been widely exploited, leading to the discovery of new bacterial vitamins and to their application in the field of animal nutrition. In this country, Dr. McIlwain showed that vitamin B_6 (pyridoxin) is essential for the nutrition of *Strep. haemolyticus*.

In continuation of these studies, Dr. McIlwain examined the action of pyridine-3-sulphonic acid and its amide: these compounds inhibited the growth of certain organisms by virtue of their relationship to nicotinic acid; they were not, however, suitable for clinical use. Dr. McIlwain also prepared amino-sulphonic acids corresponding to many aminocarboxylic acids known to be essential metabolites of bacteria, and certain of them proved, as expected, to be inhibitory to the growth of a number of organisms.

Mr. Hills studied the growth of bacteria by culturing organisms on media deficient in a single factor, and then investigating the action of the deficient factor on the metabolism of washed cells. With Morgan's bacillus, pantothenic acid (the liver filtrate factor of the vitamin B complex) was shown to catalyse oxidations involving mainly α-ketonic acids, α-hydroxy acids, the C_4-dicarboxylic acids and the dicarboxylic amino-acids. Dr. McIlwain examined homologues of pantothenic acid and found that several, in particular pantoyltaurine, were inhibitory to organisms requiring pantothenic acid for their growth.

Substances which *in vitro* were able to inhibit bacterial growth did not necessarily have a chemotherapeutic effect *in vivo*: this led to an investigation of the conditions necessary for antibacterial agents to act *in vivo*. The earlier investigations had emphasised the antagonism between naturally occurring essential metabolites and chemotherapeutic agents: it was now shown that the therapeutically effective concentration of sulphanilamide is related to the concentration of free *p*-aminobenzoic acid in the host. The majority of the acid in animals was found to be conjugated, and this appears to be of critical importance in normal sulphonamide therapy. In collaboration with Dr. F. Hawking, of the Council's staff at the National Institute (p. 203), tests were made of the *in vivo* activity of pantoyltaurine against streptococcal infections in rats: the drug was found to be effective, and inhibition of its effect, analogous to that occurring with *p*-aminobenzoic acid in sulphonamide therapy, was observed on administering pantothenate. The resistance of certain bacteria to pantoyltaurine was found to be due to their synthesis of pantothenate; this property could be varied by manipulation of the organisms independently of pantoyltaurine, and in this way drug-resistant strains of previously sensitive organisms were prepared. So great is the specificity of the antagonism between naturally occurring essential metabolite and chemotherapeutic substance, that the use of further chemotherapeutic homologues is not necessarily prevented by the development of cross-resistance in the organism.

The action of the natural antibiotic, iodinin, was investigated, and, based on this study, certain *p*-diazine di-*N*-oxides were prepared; these and other inhibitory substances were tested against strains of *Ps. pyocyanea* and *Proteus vulgaris*.

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(iii) Research in Chemical Microbiology at the School of Biochemistry, Cambridge

Medical Research Council staff:—

Miss Marjory Stephenson, Sc.D., F.R.S.
E. F. Gale, B.Sc., Ph.D.

Attached workers:—

R. Davies, B.Sc., Ph.D. (*till 1942*).
Miss H. Epps (*1941-1944*).
Miss M. E. Rowatt, B.Sc. (*since 1944*).

During the period covered by this Report, Dr. Marjory Stephenson and her co-workers at the School of Biochemistry, Cambridge, were engaged principally in biochemical studies of bacteria, and in efforts to prepare toxoids suitable for the active immunisation of man against gas gangrene toxins.

Production of Amines by Bacteria

Dr. E. F. Gale and Miss H. M. R. Epps made a detailed study of the conditions under which amines are produced by bacteria. Six bacterial enzymes (amino-acid decarboxylases) were discovered; they were prepared in a cell-free condition, and their distribution among bacterial genera and species was ascertained. These decarboxylase preparations were found useful for the accurate and rapid estimation of amino-acids in protein digests. A co-decarboxylase, common to four of the enzymes, was extracted from yeast and purified: as a result of work done at Cornell University, U.S.A., and at the Institute of Biochemistry, Cambridge, it was shown to be identical with pyridoxal phosphate.

Group D streptococci possessing high tyrosine decarboxylase activity were found in the intestinal flora of infants suffering from neonatal diarrhoea. The suggestion that this characteristic might play a part in determining the diarrhoea was strengthened by the association of streptococci of this type with four epidemics studied. The same type of streptococci, established in the intestines of infant rats, caused a fatal diarrhoea, and the syndrome could be imitated by the administration of tyramine. It was also shown that the newborn infant is deficient in tyramine oxidase activity in such tissues as the liver and kidney, the normal protective activity developing within the first 3 months of life.

In collaboration with members of the Council's staff at the National Institute it was found that, in cats, infection of the leg muscles with *Cl. welchii* resulted in a rise of the histamine content of the muscles, but not of the blood.

Active Immunisation against Gas Gangrene

The object of this work, which was begun in October, 1941, was to investigate the possibility of preparing toxoids for the active immunisation of members of H.M. Forces against the toxins of the three main gas gangrene organisms, *Cl. welchii* (*Cl. perfringens*), *Cl. oedematiens* and *Cl. septicum*. Dr. W. E. van Heyningen, Miss E. E. Sampson and Mr. R. N. Beale worked on *Cl.*

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welchii, while Dr. D. Herbert and Mrs. P. H. Herbert worked on *Cl. septicum*; at the same time, Dr. B. C. J. G. Knight and Dr. Marjorie Macfarlane were working at the Lister Institute on *Cl. oedematiens*.

Dr. van Heyningen developed a rapid method for estimating the α-toxin of *Cl. welchii*, which is based on its reaction with egg yolk solution. He succeeded in partially purifying the α-toxin, by absorption on calcium phosphate in the presence of acetone, and showed that the θ-haemolysin could be separated from the α-toxin, by absorption on red blood cells under suitable conditions. He also showed that the α-toxin is a "hot-cold" haemolysin, and that the combined haemolytic activities of α- and θ-toxins are not additive. Dr. Gale and Dr. van Heyningen studied the effect of *p*H, and of the presence of glucose during growth, on the production by *Cl. welchii* of α- and θ-toxins and hyaluronidase. Dr. van Heyningen, Miss Sampson and Mr. Beale developed methods suitable for the large-scale partial purification and concentration of the α-toxin of *Cl. welchii*, and prepared partially purified, concentrated toxoid. Dr. D. Herbert and Mrs. P. H. Herbert studied the flocculation of the lethal toxin of *Cl. septicum* and developed methods for its partial purification, concentration and toxoiding.

The toxoids of *Cl. welchii* and *Cl. septicum* thus prepared, together with *Cl. oedematiens* toxoid similarly prepared by Dr. Knight, were mixed, and then diluted with tetanus toxoid solution. The resultant polyvalent toxoid mixture was tested for its protective effect against gas gangrene infections in guinea-pigs by Dr. Muriel Robertson and Mr. J. Keppie at the Institute for Animal Pathology, Cambridge: the results obtained were promising.

The effect of iron on the metabolism of *Cl. welchii* was studied by Miss Sampson. It was shown that, when the organism is grown on an iron-deficient medium, hydrogen production is suppressed, and ethanol and acetic acid are replaced by lactic acid.

Formation of Fat in a Food Yeast

Dr. A. Kleinzeller investigated the condition of growth of the yeast, *T. lipofera*. He made a detailed biochemical study of the fat formation which occurs in this yeast, and found that the fat content varied according to conditions from 18.6 to 43 per cent. (dry weight). With the co-operation of workers for the Department of Scientific and Industrial Research at the Chemical Laboratories, Teddington, the possibility of semi-large-scale production was explored, with encouraging results. Dr. Kleinzeller intends to continue this work in Czechoslovakia.

Acetone-Butyl Alcohol Fermentation

A study of the acetone-butyl alcohol fermentation, made by Dr. Stephenson and Dr. R. Davies, showed that the production of the solvents, acetone and butanol, depends on a number of hitherto unrecognised factors in the nutrition of *Cl. acetobutylicum*, and on the age of the culture. The factors required for the nutrition of the organism are to be found in autolysed liver, maize and yeast: without them the enzymes necessary to produce the solvents are not formed, and the fermentation degenerates into a primitive acid fermentation. The production of butanol was shown to be due to the reduction of butyric acid by glucose. It was confirmed that acetic acid is a precursor of acetone in the fermentation, and that acetoacetic acid is the immediate precursor; the enzyme causing the latter transformation, acetoacetic acid decarboxylase, was prepared in a highly purified condition, and its dissociation into enzyme and coenzyme achieved.

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Biochemistry of a Cystitis Organism

A study by Dr. H. K. King of a strain of *Bact. coli,* isolated from a patient with cystitis, showed that its source of carbon was a hitherto undescribed sugar present in the urine. This sugar was highly labile and formed a characteristic osazone: its identity was not established. Dr. Stephenson and Dr. H. Waelsch found that the organism contained urease. It was thought that the urease might represent part of an adaptation to life in the bladder. This possibility was further explored. A number of strains of *Bact. coli* from cases of cystitis were examined: of 12 strains, 4 contained urease and 8 did not. Three stock strains were cultivated anaerobically in urine through 9 generations: none developed urease. Moreover, in normal urine sufficient ammonia was found to supply the nitrogen requirements of the organisms.

J. Baddiley and E. F. Gale—

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R. Davies—

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H. M. R. Epps—

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E. F. Gale—

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The production of amines by bacteria. 2. The production of tyramine by *Streptococcus faecalis*. *Ibid.*, 1940, **34**, 846.

The production of amines by bacteria. 3. The production of putrescine from *l*(+)-arginine by *Bacterium coli* in symbiosis with *Streptococcus faecalis*. *Ibid.*, 1940, **34**, 853.

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E. F. GALE—

The effect of sulphanilamide on the arginine and CO_2 requirements of Streptococci (Lancefield Group D). *Ibid.*, 1945, **26,** 234.

The estimation of *l*(+)-arginine in protein hydrolysates by the use of *l*(+)-arginine decarboxylase. *Nature, Lond.*, 1946, **157,** 265.

The bacterial amino acid decarboxylases. *Advances in Enzymology,* 1946, **6,** 1.

E. F. GALE and H. M. R. EPPS—

The effect of pH of the medium during growth on the enzymic activities of bacteria (*Escherichia coli* and *Micrococcus lysodeikticus*) and the biological significance of the changes produced. *Biochem. J.*, 1942, **36,** 600.

The influence of the presence of glucose during growth on the enzymic activities of *Escherichia coli* : comparison of the effect with that produced by fermentation acids. *Ibid.*, 1942, **36,** 619.

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Studies on bacterial amino-acid decarboxylases. 3. Distribution and preparation of codecarboxylase. *Ibid.*, 1944, **38,** 250.

E. F. GALE and W. E. VAN HEYNINGEN—

The effect of the pH and presence of glucose during growth on the production of α and θ-toxins and hyaluronidase by *Clostridium welchii*. *Biochem. J.*, 1942, **36,** 624.

W. E. VAN HEYNINGEN—

The biochemistry of the gas gangrene toxins. 1. Estimation of the α-toxin of *Cl. welchii*, Type A. *Biochem. J.*, 1941, **35,** 1246.

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H. K. KING—

Biochemistry of a cystitis organism, 1 and 2. *Biochem. J.*, 1942, **36,** 43.

A. KLEINZELLER—

Fat formation in *Torulopsis lipofera*. *Biochem. J.*, 1944, **38,** 480.

M. ROBERTSON and J. KEPPIE—

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E. S. TAYLOR and E. F. GALE—

Studies on bacterial amino-acid decarboxylases. 6. Codecarboxylase content and action of inhibitors. *Biochem. J.*, 1945, **39,** 52.

CHEMOTHERAPY

Research in Chemotherapy at the Molteno Institute, Cambridge

Staff:—

Miss Ann Bishop, Sc.D., D.Sc., Ph.D.

Attached workers:—

Miss B. M. Gilchrist, B.Sc. (*1943-45*).
Miss B. Birkett, B.Sc. (*from March, 1945*).

In the Molteno Institute, Cambridge, directed by Professor D. Keilin, Dr. Ann Bishop and her colleagues were engaged throughout the war in testing new synthetic drugs for antimalarial activity. Dr. Bishop, who

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formerly had a grant from the Council, became a member of their whole-time research staff in 1942. A large number of new compounds has been tested, but, although some of these have been very successful in suppressing or even curing infections of *Plasmodium relictum* induced in canaries by the inoculation of infected blood, none so far has been effective in preventing infections induced by sporozoites (*i.e.*, by mosquito transmission). As it was realised that the technical experience gained at the Molteno Institute would be of value to others working in the same field, Dr. Bishop prepared a comprehensive monograph dealing with research methods in relation to the chemotherapy of avian malaria; this was published in *Parasitology* in 1942.

In addition to chemotherapeutic tests, research has been continued upon fundamental problems of the biology of the malaria parasite and its insect host. A seasonal fluctuation in the number of gametocytes produced by a strain of *P. relictum* in canaries was observed, the average number being higher from April to July than at other times of the year.

As a preliminary to the study of the conditions of survival of sporozoites (the infective stage of the malaria parasite in the mosquito) and their possible growth in tissue-culture, Dr. Bishop and Miss Gilchrist have devised a method for obtaining sporozoites of *P. gallinaceum* free from the tissues of the salivary glands of the mosquito, by feeding infected mosquitoes (*Aëdes aegypti*) through prepared animal membranes upon uninfected blood. The sporozoites are ejected from the proboscis of the insect into the blood during the act of feeding. Similarly, mosquitoes can be infected with malaria by inducing them to feed upon infected blood. This membrane technique has also been used in studying the factors which attract mosquitoes to their food. It has been proved that gorging is provoked by a heat gradient between the environment and the food-limiting membrane. The different methods of feeding used by mosquitoes were studied, and the results confirm that the nature of the food, not the method of its intake, determines its destination, whether directly to the stomach or into the diverticula of the mosquito.

By the use of an amputation technique, Dr. Bishop and Miss B. Birkett have studied the function of the antennae of the mosquito in locating food: the results so far obtained suggest that this may be associated with heat perception.

With Miss Gilchrist, and later Miss Birkett, Dr. Bishop has studied the effect of prolonged treatment with quinine, mepacrine, pamaquin and sulphadiazine upon infections of avian malaria (*P. relictum* in canaries and *P. gallinaceum* in chickens). The object has been to obtain information about the factors determining eradication of blood-inoculated infections, and about the part played by exo-erythrocytic forms in relapse and in the development of immunity.

A. Bishop—

Chemotherapy and avian malaria. *Parasitology*, 1942, **34**, 1.

Variation in gametocyte production in a strain of *Plasmodium relictum* in canaries. *Ibid.*, 1943, **35**, 82.

A. Bishop and B. M. Gilchrist—

A method for collecting sporozoites of *Plasmodium gallinaceum* by feeding infected *Aëdes aegypti* through animal membranes. *Nature, Lond.*, 1944, **153**, 713.

Experiments upon the feeding of *Aëdes aegypti* through animal membranes with a view to applying the method to the chemotherapy of malaria. *Parasitology*, 1946, **37**, 85.

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The Department for Research in Industrial Medicine, London Hospital

Medical Research Council staff and attached workers:—

Donald Hunter, M.D., F.R.C.P. (*Physician-in-Charge*).
K. M. A. Perry, M.D., M.R.C.P.
J. N. Agate, M.B., M.R.C.P. (*from Feb., 1945*).
N. L. Spoor, B.Sc., Ph.D. (*1943-1945*).
R. F. Milton, B.Sc., F.R.I.C. (*1943-1945*).
J. Graham, B.Sc., Ph.D. (*till Aug., 1944*).
Miss H. M. B. Buckell, B.Sc. (*from Jan., 1944*).
Miss M. E. Thompson, B.Sc. (*1943-1944*).
H. A. Druett, B.Sc. (*from Jan., 1944*).
Miss Jessie Garrad, B.Sc. (*from April, 1945*).
I. Leslie, B.Sc. (*from Nov., 1944*).
R. G. Bowler, B.Sc. (*from May, 1945*).
Miss Doris M. Thornton, M.A.

In June 1943 the Council established the Department for Research in Industrial Medicine, under the part-time direction of Dr. Donald Hunter, at the London Hospital. The primary function of the Department is to undertake research into the prevention and treatment of disorders affecting industrial workers, including both occupational diseases and others of a more general kind; the Department is also concerned with problems of the rehabilitation and suitable placement in industry of physically handicapped workers. The situation of the Department in a large teaching hospital has the advantages not only of ready access to patients, but also of making readily available the advice and experience of experts in other branches of medicine; special acknowledgment is due to Dr. M. H. Jupe, Director of the Radiodiagnostic Department of the Hospital, for his co-operation in many of the studies outlined below. In addition to work done actually within the Hospital, the research programme of the Department has involved numerous field investigations in factories and elsewhere.

Industrial Dusts

Dusts in iron and steel foundries, and in iron turneries.—In iron foundries, workers are exposed to iron oxide, which produces changes in the lungs indistinguishable from silicosis, as well as to silicates and quartz. With the co-operation of the Factory Department of the Ministry of Labour, a large-scale investigation, involving the X-raying of over 2,000 workers, was undertaken into the incidence of silicosis and other pulmonary abnormalities due to dust in iron and steel foundries. It was shown that in the steel-foundry workers the incidence both of silicosis and of other radiological abnormalities due to dust was about twice as high as that noted in men working in iron foundries. Various environmental studies have been undertaken, but more research is necessary to determine the exact nature of the responsible dust. Similar studies, but on a smaller scale, have been made on workers in iron turneries, and on bath enamellers.

Aluminium dusts.—An inquiry into the potential hazards from alumina dust in a factory, carried out on behalf of the Council in 1936, had revealed no deleterious effects on the workers. Further investigations on the subject were considered desirable, however, in view of published work from Canada on the use of aluminium dusts for the prevention and treatment of silicosis,

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and of the apparently contradictory finding in Germany that an acute pneumokoniosis was common in workers making aluminium powder. Studies were accordingly undertaken by the Department on the effects of aluminium and alumina dusts on the grinders of duralumin aeroplane propellers. X-ray investigations, and analysis of the previous year's illnesses of 90 workers exposed to the dusts, disclosed no ill-effects which could be related to their occupation. At the time of this report, the nature and causation of the pneumokoniosis in the German aluminium workers was being explored in Germany by Major M. C. S. Kennedy, with whom the Department were in touch. With the co-operation of Dr. L. W. Hale, a trial has been arranged of the value of aluminium therapy for silicosis in Cornish tin-miners. Environmental studies have also been undertaken in one of the mines concerned.

Bagasse dust.—A special type of respiratory disease studied was that due to bagasse dust. Bagasse, the dried sugar-cane fibre from which the sugar has been extracted, was imported from Louisiana in large quantities during the war for the manufacture of thermal and acoustic insulating board. The tightly-packed bales, as brought by ship to this country, had often to be broken open and shredded under " black-out " conditions and when, as a sequel to enemy air attacks, there was insufficient water available for damping down the dust. Under such conditions the dust constituted a serious hazard, and as many as 10 out of 21 men engaged in handling bagasse for more than three days during a period of 15 months developed bronchiolitis and pneumonia. In most cases the onset of the illness occurred some eight weeks after starting work on the shredding machines. Two patients have died in the series reported, but the majority recovered completely within six weeks.

Industrial Toxicology

Poisonous metals and their salts.—In precious metal refineries examples of poisoning with complex salts of platinum, causing a respiratory syndrome, and with osmium tetroxide fumes, producing bronchitis and transient blurring of vision, were investigated, and appropriate precautions were recommended. The hazard of chronic mercury poisoning was studied in a thermometer workshop and in chemical works; many of the thermometer makers were found to be suffering from mild mercurialism, and it was suggested that this was due, at least in part, to absorption of the metal through the skin.

When the production of uranium became of military importance towards the end of 1943, the Department collaborated with Dr. A. Thelwall Jones in keeping under constant supervision all the workers who were handling the material in this country; this task was undertaken in response to a request to the Council from the Department of Scientific and Industrial Research on behalf of " Tube Alloys ".

Fluorides.—Following a request transmitted to the Council by the Department of Health for Scotland, an investigation was carried out in an aluminium works in which a risk of fluorosis had been indicated by the observation of the poor condition and dental deformity of the cattle and sheep in the vicinity, which had eaten grass contaminated with fluoride dust from the factory. The occurrence of fluorosis in the sheep and cattle was confirmed, and clinical, radiographic and biochemical studies were made to determine the incidence and possible effects of fluorosis in workers at the factory, and in persons living in the neighbourhood. A report on the findings is being published.

A similar investigation was carried out in a magnesium foundry in which fluoride fluxes were used to minimise the risk of fire.

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Inorganic compounds of arsenic.—Following a statistical study by Professor Bradford Hill (p. 326), of the incidence of neoplastic disease among workers with arsenic in a factory, the Department carried out observations on the atmospheric content of arsenic in the factory concerned, and examined those of the workers who had been handling arsenic and sulphur. Accounts of the statistical and other observations are being published.

Phosphine.—The risk from phosphide dust and gaseous phosphine during the processes of manufacturing life-saving flares was investigated, and some cases of transient poisoning were observed. No evidence was found of any persistent damage to the blood-forming system, and it is probable that previous findings of its occurrence may have been due to the presence of arsine as a contaminant of the phosphine.

Other industrial poisons.—Among other investigations carried out by the Department in regard to industrial poisons were studies of the risks of benzene intoxication in workers using aeroplane dope and industrial rubber solvents, of the skin damage that can result from methyl bromide, which has been used extensively as an insecticide and as a fire extinguisher, and of an acute toxic polyneuritis occurring in workers in the plastic industry manufacturing tricresyl phosphate; in this last instance the method of entry of the poison to the body was almost certainly by absorption through the skin.

Vascular Effects of Vibrating Tools

The use of vibrating tools driven by compressed air or electrically, and the operations involved in grinding metal castings against large grinding wheels, have been found to produce vascular disturbances of the hands, resulting in local pallor, weakness and stiffness of the fingers; occasionally these changes have been so severe as to prevent men from continuing their occupation. The Department investigated the condition in a group of pneumatic tool workers, including rivetters, caulkers, fettlers and others, and found these vascular phenomena to be of frequent occurrence. The syndrome usually developed after 2-5 years of such work, and was most frequent when tools with a vibration rate of 2,000-3,000 per minute were used; it occurred most often in cold weather, and cold was probably a precipitating factor. Further studies have led to the development of accurate methods for recording and analysing the vibrations produced by a tool while in operation, and this has permitted detailed studies of individual instruments, with a view both to determining the risks attached to their use, and to indicating where improvements of design are desirable.

As observers in Germany had reported that arthritis was liable to follow the use of vibrating tools, the joints of the workers were X-rayed: arthritic changes were found to be rare.

The Employment of the Physically Disabled in Industry

An important part of the work of the Department has been the study of the rehabilitation and settlement in industry of persons suffering from disabilities of different types. Special attention has so far been given to patients with heart disease, and it has been found possible by careful job selection to retain a high proportion of them in industry, under conditions in which they can work as satisfactorily as normal individuals. Suitable settlement of disabled workers is naturally a more difficult problem in small than in larger firms, and follow-up studies showed that, under existing arrangements, less

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than 10 per cent. of the disabled employed by small firms were satisfactorily placed with regard to their disabilities. Close liaison between the hospitals and the Disablement Rehabilitation Officers of the Ministry of Labour will be necessary to ensure satisfactory placing in such cases.

J. N. AGATE and H. A. DRUETT—
A method for studying vibrations transmitted to the hands. *Brit. J. industr. Med.*, 1946, **3**, 159.

J. N. AGATE, H. A. DRUETT and J. B. L. TOMBLESON—
Raynaud's phenomenon in grinders of small metal castings. *Brit. J. industr. Med.*, 1946, **3**, 167.

M. BUCKELL, J. GARRAD, M. H. JUPE, A. I. G. MCLAUGHLIN and K. M. A. PERRY—
The incidence of siderosis in iron turners and grinders. *Brit. J. industr. Med.*, 1946, **3**, 78.

M. BUCKELL, D. HUNTER, R. MILTON and K. M. A. PERRY—
Chronic mercury poisoning. *Brit. J. industr. Med.*, 1946, **3**, 55.

E. C. B. BUTLER, K. M. A. PERRY and J. R. F. WILLIAMS—
Methyl bromide burns. *Brit. J. industr. Med.*, 1945, **2**, 30.

H. A. DRUETT and J. MC.G. SOWERBY—
An apparatus for the maintenance of a carbon dust cloud of constant concentration. *Brit. J. industr. Med.*, 1946, **3**, 187.

D. HUNTER—
Industrial toxicology. *Quart. J. Med.*, 1943, **12**, 185.
Discussion on the clinical approach to industrial medicine. *Proc. R. Soc. Med.*, 1943-44, **37**, 241.
Recent advances in industrial medicine. *Practitioner*, 1945, **155**, 270.

D. HUNTER, A. I. G. MCLAUGHLIN and K. M. A. PERRY—
Clinical effects of the use of pneumatic tools. *Brit. J. industr. Med.*, 1945, **2**, 10.

D. HUNTER, R. MILTON and K. M. A. PERRY—
Asthma caused by the complex salts of platinum. *Brit. J. industr. Med.* 1945, **2**, 92.

D. HUNTER, R. MILTON, K. M. A. PERRY, H. J. BARRIE, J. F. LOUTIT and T. S. MARSHALL—
Investigation for signs of benzene intoxication in workers using aeroplane dope and rubber solvents. *Brit. J. industr. Med.*, 1944, **1**, 238.

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Effect of aluminium and alumina on the lung in grinders of duralumin aeroplane propellers. *Brit. J. industr. Med.*, 1944, **1**, 159.

D. HUNTER and K. M. A. PERRY—
Bronchiolitis resulting from the handling of bagasse. *Brit. J. industr. Med.*, 1946, **3**, 64.

D. HUNTER, K. M. A. PERRY and R. B. EVANS—
Toxic polyneuritis arising during the manufacture of tricresyl phosphate. *Brit. J. industr. Med.*, 1944, **1**, 227.

A. I. G. MCLAUGHLIN, R. MILTON and K. M. A. PERRY—
Toxic manifestations of osmium tetroxide. *Brit. J. industr. Med.*, 1946, **3**, 183.

R. MILTON—
An absorptiometric method for the estimation of atmosphere benzene. *Brit. J. industr. Med.*, 1945, **2**, 36.

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Research in Industrial Physiology at the London School of Hygiene and Tropical Medicine

(i) *Medical Research Council staff:—*

T. Bedford, D.Sc., Ph.D., M.I.Min.E.
C. G. Warner, B.Sc., Ph.D. (*till 1944*).
C. N. Davies, M.Sc., F.Inst.P. (*since 1945*).
F. A. Chrenko (*since 1941*).
N. L. Spoor, B.Sc., Ph.D. (*1943*).
F. E. Smith (*since 1945*).

(ii) *Medical Research Council staff:—*

H. C. Weston, F.I.E.S.

(i) *Studies of Ventilation, Environmental Warmth, and Industrial Dusts*

Ventilation.—Before the outbreak of war, investigations had been carried out by Dr. T. Bedford, Mr. F. A. Chrenko and Dr. C. G. Warner on the natural ventilation of dwellings, and much information had been collected on the effect of air gratings, flues, fires, wind speed, and other factors in the rate of change of air in rooms: an account of the main findings of these investigations was published in 1943, to assist those concerned with the planning of homes in the post-war period.

From 1940 onwards Dr. Bedford and his colleagues carried out observations on the ventilation of public, and other, air-raid shelters at the request of the authorities concerned and advised on the measures for their improvement. Special investigations were made on atmospheric pollution in Royal Ordnance Factories, in relation to the risks of T.N.T. and tetryl poisoning. The atmospheric content of T.N.T. under different conditions was determined, and a figure was suggested for the maximum safe concentration of T.N.T. in the air. Specially high levels were noted at night under " black-out " conditions, and measures had to be devised to deal with this problem. It was found possible to introduce improvements in ventilation and in filling methods which greatly enhanced the comfort, and probably the efficiency, of the workers and reduced the risks of poisoning. Corresponding work was carried out for the Air Ministry and Ministry of Labour on the ventilation of aircraft factories, especially in aircraft doping rooms.

Measurement of environmental warmth.—It was found during the war that the methods commonly used for the measurement of environmental warmth were not fully adequate when very high temperatures were experienced and when radiation from hot surfaces was also high. Such conditions were frequently experienced in H.M. ships in the tropics, in ships' boiler rooms and in foundries. Dr. Bedford undertook an investigation of the subject on behalf of the Royal Naval Personnel Research Committee (p. 147), and introduced a method of measurement which made a reasonable allowance for radiant heat. Basing the method on the scale of " effective temperature " devised by the American Society of Heating and Ventilating Engineers, which takes into account the factors of dry-bulb temperature, wet-bulb temperature and air velocity, the correction recommended was the use of the globe-thermometer temperature-reading instead of the air temperature on the dry-bulb thermometer scale. The results of this work have been published in the Council's series of War Memoranda under the title " Environmental Warmth and its Measurement ": the Memorandum is accompanied by a series of alignment charts that make it possible to carry out the necessary calculations with a minimum of trouble.

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Dust sampling instruments.—As a result of their studies on the dust hazard in coal mines, Dr. Bedford and Dr. Warner had recommended that the thermal precipitator should be regarded as the standard dust sampling instrument. They realised, however, the necessity of investigating the efficiency of other types of sampler, and basic research on the subject was undertaken by Mr. C. N. Davies. Data on the sedimentation of spherical particles have already been published and information on non-spherical particles is being accumulated. Light extinction methods of measurement of dust are under investigation, and, for the testing of sampling apparatus, methods of setting up clouds of spheres of approximately uniform size are being developed.

T. Bedford—

Factory ventilation under war conditions. *Industr. Welf.*, 1939, **21**, 421.

The problem of night work. *Ibid.*, 1939, **21**, 427.

Ventilation and heating in relation to human comfort. *J. Inst. Heat. Vent. Engrs*, 1939, **7**, 377.

The present status of industrial hygiene in Great Britain. *Proc. Pacif. Sci. Congr. Ass., 1939*, 1943, **6**, 1.

Lung disease in coal miners: a review. *Fuel*, 1943, **22**, 129.

Industrial ventilation in war. *Bull. Hyg.*, 1943, **18**, 91.

Heating and ventilation: Requirements and methods. *Brit. J. industr. Med.*, 1944, **1**, 31.

Ventilation of dwellings. *J. R. sanit. Inst.* 1945, **65**, 100.

Environmental warmth and its measurement; with Supplement. *M.R.C. War Memorandum* No. 17, London, 1946.

T. Bedford and H. E. Collier—

Continued discussion on night work. *Industr. Welf.*, 1939, **21**, 471.

T. Bedford and C. G. Warner—

Subjective impressions of freshness in relation to environmental conditions. *J. Hyg., Camb.*, 1939, **39**, 498.

Measurements of concentrations of air-borne dusts. *J. industr. Hyg. Toxicol.*, 1942, **24**, 315.

T. Bedford, C. G. Warner and F. A. Chrenko—

Observations on the natural ventilation of dwellings. *J. R. Inst. Brit. Architt.*, 1943, **51**, 7.

C. N. Davies—

A capillary viscometer with variable rate of shear. *Rev. sci. Instr.*, 1945, **16**, 98.

Definitive equations for the fluid resistance of spheres. *Proc. Phys. Soc., Lond.*, 1945, **57**, 259.

Early observation of antibiotic action. *Nature, Lond.*, 1945, **156**, 666.

C. G. Warner—

Measurements of the ventilation of dwellings. *J. Hyg., Camb.*, 1940, **40**, 125.

Dust reduction at the coalface by means of water sprays. *J. industr. Hyg. Toxicol.*, 1943, **25**, 303.

(ii) *Lighting and Vision*

In the early months of the war the advice of the Council was sought in regard to the lighting of factories, and a memorandum was prepared by Mr. H. C. Weston on work in natural and artificial light, at the request of an Interdepartmental Committee under the Chairmanship of Lord Knollys. The introduction of " black-out " conditions, and of extensive night-shift work, raised important questions regarding the health, efficiency, and morale of

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factory workers. No standards of lighting had been defined under the Factories Act of 1937 and on this point advice was given, it being considered that these must be more generous than in peace time and that a higher standard should be prescribed for continuous fine work. It was recognised that artificial light sources would be more acceptable if rendered unobtrusive and, if possible, giving the appearance of daylight. For this purpose the tubular fluorescent lamp provided the suitable means and, in a factory in which the subject was first studied, these lamps, placed in false windows in the positions occupied by the real but obscured windows, produced the desired " daylight " effect.

The Home Office Departmental Committee on Lighting in Factories, of which Mr. Weston was a member, in submitting their fifth Report in June, 1940, made recommendations on standards of lighting, on the basis of which the Factories (Standards of Lighting) Regulations, 1941, under Section 5 of the Factories Act, 1937, were drafted. In connection with this work, Mr. Weston served on a number of Committees.

Throughout the war Mr. Weston gave much advice on specific problems of illumination as they arose in factories and other places concerned with essential war services.

The results of an investigation by Mr. Weston on the effect of brightness contrast on the difficulty of visual tasks, and the illumination required according to the degree of contrast, were published in 1945, as *Industrial Health Research Board Report* No. 87. Other work included a report on maximum permissible standards of illumination (to economise electricity), and an inquiry into the illumination requirements of post-war buildings, undertaken on behalf of a Committee appointed by the Building Research Board and under the aegis of the Ministry of Works.

H. C. Weston—

Eyestrain in factories. *Aircraft Production*, 1940, **2**, 81.

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The Applied Psychology Research Unit, Cambridge

(including work done by members of the Council's staff at the Psychological Laboratory, Cambridge, before the Unit was established)

Director of the Psychological Laboratory; Honorary Director of the Unit from May, 1945:—

Professor F. C. Bartlett, C.B.E., M.A., F.R.S.

Medical Research Council staff and attached workers:—

K. J. W. Craik, Ph.D. (*Director of the Unit, 1944-45*).
E. Farmer, M.A.
E. G. Chambers, M.A. (*temporarily seconded to Air Ministry*).
Miss M. D. Vernon, M.A.
N. H. Mackworth, M.B.
D. Russell Davis, M.D., M.R.C.P., D.P.M.
R. B. Buzzard, B.M. (*temporarily seconded to Air Ministry*).

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Miss Alice W. Heim, Ph.D.
W. H. N. Hotopf, B.A. (*temporarily seconded to War Office, from 1941*).
J. W. Whitfield, B.A.
Mrs. H. Himmelweit (*April—October, 1943*).
Miss N. Timpany, B.Sc.
Mrs. Sheila J. Macpherson.
J. W. McFie, B.A.
Miss E Margaret Milbanke (*till* May, *1944*).
W. E. Hick, M.B. (*from Nov., 1944*).
Miss V. C. Stone, B.Sc. (*from Oct., 1944*).
Miss Evelyn M. Smith (*Sept., 1944—Sept., 1945*).
Lady I. M. Frankau, M.D.
M. H. Pirenne (*Lieutenant, Belgian Army; 1942-45*).
R. B. Bromiley (*Lieutenant, R.C.A.M.C.; 1941-42*).

For many years before the war Mr. Farmer and Mr. Chambers, both members of the Council's staff working for the Industrial Health Research Board, had been engaged in developing practical tests for vocational selection and accident proneness at the Psychological Laboratory, Cambridge University, directed by Professor Bartlett; more recently they had had the co-operation of Dr. Alice Heim and Mr. Hotopf in similar studies. On the outbreak of war, the team at the Laboratory speedily became involved in investigations on behalf of the Fighting Services, especially the Flying Personnel Research Committee of the Air Ministry (p. 132), or otherwise directly related to the national emergency. As this work grew in range and in practical importance it became necessary to reinforce the staff engaged upon it, and early in 1944, with the concurrence of the University, the Council established a Unit for Research in Applied Psychology at Cambridge, Dr. Kenneth J. W. Craik being appointed its first Director. His brilliant experimental abilities and his power of leadership led to rapid developments of the work in many directions. A year later Dr. Craik was killed in a traffic accident. It was a most severe blow, but by now the Unit was well established and its work has continued with much success along the lines which he had marked out. The chief items of the research programme of the team during the war may be grouped as follows:—

(1) Personnel selection for the Fighting Services and for industry.
(2) Technical experimental studies, especially concerned with:
(*a*) the development of methods for determining the effects of "harassing agents".
(*b*) the effects of certain drugs, particularly of the amphetamine group.
(*c*) nutritional problems.
(*d*) experimental investigations of skill fatigue.
(*e*) problems of "display" and "control".
(*f*) accidents and accident prevention.
(*g*) problems of rehabilitation.

Personnel Selection

At the beginning of hostilities, Mr. Farmer, who had already carried out a number of experiments in vocational selection for the Fighting Services, made contact with the War Office and arranged for a large-scale trial of methods designed to match the intelligence requirements of various branches of Army Service with the intelligence equipment of available recruits. At this stage the time officially allowed for this type of test was strictly limited and it was possible to use only somewhat abbreviated pen and paper tests of the verbal intelligence type and for the assessment of mechanical ability. Mr. Farmer was first assisted by Mr. Chambers and Mr. Hotopf, and later by Mr. A. Rodger, Mr. J. G. W. Davies and Mr. E. Anstey. As the work

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developed a stage was reached when it was regarded as having passed beyond the phase of an experimental " try-out ". In 1941 a Directorate for Selection of Personnel was set up by the War Office, and several of the original investigators were taken over by the Army. The Directorate further developed and modified the methods of selection. In the meantime the methods adopted by members of the team at Cambridge had resulted in the collection of much valuable information concerning the range of intelligence required in a very large number of trades, vocations and professions of civil life. Some of this has been analysed and published in a paper by Mr. Whitfield and Mrs. H. Himmelweit referred to below.

In much the same way, all the early personnel selection tests and methods used by the R.A.F. were developed in the Cambridge Laboratory. Initial verbal and mathematical tests of intelligence were devised and standardised by Mr. Chambers, and were widely applied to Royal Air Force pilot candidates. These tests, also, in due course passed beyond the experimental stage, and, in a more completely developed form, became an official concern of the R.A.F. itself. Mr. Chambers was seconded to the Air Ministry for whole-time work on behalf of the Flying Personnel Research Committee from October, 1939.

Before the war, Group Captain G. C. Williams, R.A.F., had been developing at Cambridge a possible mechanical performance test for air pilots. With the co-operation of Mr. Farmer and Mr. Chambers, he designed a sensori-motor instrument test, using an appliance which, in the form known as S.M.A.3, became subsequently a standard test apparatus for air pilots throughout the whole Empire flying service. The first of these instruments was built by Dr. E. J. H. Schuster, of the Council's staff (p. 203).

Later such personnel selection studies as remained part of the programme of the group at Cambridge became much more highly specialised. For example, workers for the Council shared in a highly successful development of special selection methods use to pick R.A.F. Control Room and Filterer personnel. A large-scale enquiry into the possibility of selection based chiefly upon the assessments of qualities of temperament and character owed much to Dr. Russell Davis, Mr. Chambers and Miss Vernon.

Side by side with these researches on selection problems for the Fighting Services went much similar work, directed principally by Dr. Heim, which dealt with selection for particular tasks in industry. Experiments were carried out at certain Labour Training Centres, but, in spite of promising results, they received only limited recognition. More practically effective was a series of investigations made in various factories engaged upon war work; not only was the technique of large-scale intelligence testing much developed, and some of its difficulties more fully realised and faced than hitherto, but a noteworthy degree of success was achieved in determining aptitudes for the practical operations of machine manipulation, and for general inspection work. A beginning of some promise was made in the validation of selection methods for foremen.

Technical Experimental Studies

(a) " *Harassing agents* ".—Early in the war Dr. Mackworth, working temporarily at the Chemical Defence Research Experimental Station, Porton, established some new methods for assessing the psychological effects of " harassing agents ", such as tear gases and arsenical smokes.

(b) *Drugs*.—Dr. Mackworth and Dr. Russell Davis carried out experiments for all three of the Fighting Services and Personnel Research Committees (pp. 131-152), which determined definitely the limits of usefulness of analeptic drugs of the amphetamine-ephedrine group as temporary aids to operational

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efficiency. Practical rules for the administration of such drugs, drawn up on the basis of these and other tests, were accepted by the Service Departments.

(c) *Nutritional Studies.*—Dr. I. M. Frankau (Lady Frankau) held a grant from the Council for work upon the possible effects of vitamin supplements in relation to the physical efficiency and endurance of healthy young adults, mostly aircrew cadets. Evidence was obtained of a favourable effect of nicotinamide upon efficiency—presenting, apparently, an interesting example of a vitamin acting as a drug. Later, Lady Frankau joined the group of workers engaged in studies of vitamin C deficiency at Sheffield (p. 109).

(d) *Fatigue.*—Special attention was given by the team at Cambridge to problems incidental to fatigue following upon long periods of highly skilled work such as flying " blind " at night. For these studies the apparatus known as the " Cambridge Cockpit ", designed by Dr. Craik and built at the Laboratory, proved invaluable; in internal lay-out it closely resembles the cockpit of an aircraft. Dr. Russell Davis was particularly responsible for demonstrating the essential temperamental basis of many of the fatigue effects noted in the subjects tested by this and other means, and also of the related liability to accidents.

(e) *" Display " and " Control ".*—Every machine, when working, presents certain signals for action which the operator must interpret, and possesses parts such as levers, switches, wheels and so on, which he must manipulate in response to these signals. The general name for the methods by which such signals are presented visually to the operator is " display ", and that for the resultant action, and the means by which it is effected, " control ". If either is planned without regard to the needs and capabilities of the greatest number of ordinary operators, a tremendous amount of inefficiency, fatigue, nervous strain, accidents and spoiled work is bound to follow. The problems which have to be considered are many and diverse, and require for their solution a combination of psychological, physical and engineering skills. Under the guidance of Dr. Craik, these problems became more and more the main pre-occupation of the Unit; they raise fundamental questions about perception, the mechanics of bodily movement, and the exercise of human judgment. Craik's own work covered all these fields, but was especially influential in regard to a large variety of problems of visual adaptation, and particularly of vision under poor conditions of illumination. He was assisted throughout by Mrs. S. Macpherson and latterly by Dr. Hick. Dr. Hick has since extended the study of " control " problems. He has demonstrated the best kind of equipment to use with " jolting " conditions, has examined several problems of rifle aiming, has investigated a number of different tracking systems and has shown the effects of a varying resistance when steady winding is required. This work is actively continuing.

A number of visual studies, especially at the level of complex perception, were carried out by Miss Vernon, partly in collaboration with Dr. Craik and partly independently. Notable among these was an investigation of the conditions necessary for the quick and accurate reading of dials and banks of dials. The results of this work have already had many valuable applications in dial design.

Dr. Mackworth directed some studies which had an immediate practical effect on the design and equipment of R.A.F. Control Rooms, and towards the end of the war the same worker, together with Dr. A. Carpenter, carried out extensive investigations, which still continue, on the effects upon human behaviour of high temperature and humidity. This work is being done for the Royal Naval Personnel Research Committee (p. 147).

(f) *Accidents and Accident Prevention.*—Mr. Farmer and Mr. Chambers have maintained their interest in the study of accident prevention. It was

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difficult during the war period to secure adequate conditions for properly controlled experiment, or for the collection of the necessary statistics for analysis. However, work is still continuing, with a rather better prospect of progress in the immediate future. Dr. Russell Davis's studies of temperament in relation to flying accidents had a more definite practical issue, and towards the end of the war Mr. Whitfield, working mainly from a statistical angle, introduced new methods of promise, especially in relation to a study of certain types of mining accidents.

(g) *Rehabilitation.*—Dr. Heim and Miss A. Rennison began some studies of rehabilitation problems, at first with the Wound Infection Research Unit at Birmingham (p. 266) and more lately with the newly established South Wales Pneumokoniosis Unit (p. 158). Dr. Buzzard, working first as an investigator for the Council, and later seconded to the Air Ministry, carried out extensive and effective investigations into the reposting of aircrew due for remuster, and the rehabilitation in the R.A.F. of flying personnel who were returned prisoners of war.

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E. FARMER—

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I. M. FRANKAU—
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A. W. HEIM—
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W. E. HICK—
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H. T. HIMMELWEIT and J. W. WHITFIELD—
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N. H. MACKWORTH—
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M. H. PIRENNE—
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J. W. WHITFIELD—
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Research in Industrial Psychology, Manchester

Medical Research Council staff and attached workers:—

S. Wyatt, D.Sc.
R. Marriott, M.Sc.
Norah M. Davis, M.A.
W. M. Dawson, B.Sc.
D. E. R. Hughes.
F. G. L. Stock.

Reference has been made on pp. 153 and 156 to the studies by Dr. Wyatt and his colleagues of the effects on health and efficiency of the excessively long hours of work voluntarily endured by industrial operatives during the period of acute national emergency which followed the evacuation from Dunkirk. It was found that, towards the end of June, 1940, the outburst of energy and enthusiasm, with improved output, which characterised the first few weeks of the emergency period, was giving place to lassitude, staleness, increased sickness absence and a fall in output. On the basis of the information collected, which was later summarised in *Industrial Health Research Board Emergency Report* No. 2, it was officially accepted from the end of July, 1940, that, over an extended period, the weekly hours of work for men and women should not exceed 60 and 55, respectively. The beneficial effects of this reduction in working hours, together with the introduction of staggered holidays, were reflected in better time-keeping, improved health and revived enthusiasm.

At about this period of the war there was much uninformed criticism of the amount of absenteeism particularly among women in industry. Accordingly, at the request of the Ministry of Supply, a statistical survey was made of the extent and distribution of " absence " in random samples of women workers in two Royal Ordnance Factories over a period of six weeks. The

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results, which were published in *Industrial Health Research Board Emergency Report* No. 4, showed that very few women were habitually absent for one or two shifts in each week, and that the great majority of the " absences " were of varying length, at irregular intervals. Thus, whatever the main causes of absence from work, they were not regularly recurrent but were as varied as individual needs and circumstances. This suggested the need for a study of the personal causes of absence, and for an " individual " method of dealing with them—a policy which was subsequently adopted with increasing success.

In the latter part of 1942 a further reduction in the weekly hours of work was made in a number of factories engaged on war production, and though the extent of the reduction was sometimes small, it was thought that it might have a measurable effect on output. The results of an investigation on groups of workers in different factories showed that, in the few instances in which it was possible to separate the effects of shorter hours from those of other conditions, the reduced working hours had led to a small but definite improvement in hourly output. In most of the factory groups, however, any relation between hours and output was obscured by the much greater influences of changes in the type or design of product manufactured, mechanical difficulties, variations in the quantity and quality of the materials used, progressive improvements in the methods or conditions of work, changes in the type or lay-out of machines, and personal factors such as dissatisfaction with the method or rate of payment. The inquiry, of which an account was published as *Industrial Health Research Board Emergency Report* No. 5, provided some indication of the relative importance of these different factors for both the work and the workers.

In 1942-43 a survey was made of the amount, distribution and nature of certified sickness absence in some 20,000 women industrial workers. The absence rate was found to be highest in the age group 30-50, and the amount of sickness absence of married women exceeded that of single women by 65 per cent. This much greater incidence of sickness absence among the married women was attributable not only to the extra effort involved in running a home, but also to anxiety for husbands and sons on war service, and to the break-up of family life so commonly caused by the war. Functional nervous disorders (including " fatigue ") ranked high among the causes of sickness absence. The investigation showed, incidentally, the great value of complete and accurate records of sickness absence as an index of industrial health.

This statistical study of sickness absence, published as *Industrial Health Research Board Report* No. 86, was followed by an inquiry into the predisposing causes of ill-health among women in industry, in which groups of women with high and low incidences of sickness absence, respectively, were interviewed in order to ascertain their personal attitudes to various factors both inside and outside the factory; the findings were published in *Industrial Health Research Board Report* No. 88. Among the many points brought out in the survey, which cannot be detailed here, was the widespread, though not universal, unpopularity of night-work; only about one-third of the women interviewed liked working at night, about 40 per cent. of those on night work spent not more than six hours of the twenty-four at rest in bed, and there was other evidence that night work imposed extra physical and mental strain, largely owing to the dislocation of normal eating and sleeping habits. An appendix to the Report deals with the question of the popularity of the factory canteens, and the extent to which these were used by the women workers. Dr. B. McArdle (p. 256) co-operated in this study, by interviewing many of the women from the medical standpoint.

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INDUSTRIAL HEALTH RESEARCH BOARD—
Hours of work, lost time and labour wastage. *Industr. Hlth Res. Bd, Lond., Emergency Report* No. 2, 1942.

S. WYATT, R. MARRIOTT and D. E. R. HUGHES—
A study of absenteeism among women. *Industr. Hlth Res. Bd, Lond., Emergency Report* No. 4, 1943.

S. WYATT, assisted by R. MARRIOTT, W. M. DAWSON, D. E. R. HUGHES and F. G. L. STOCK—
A study of variations in output. *Industr. Hlth Res. Bd, Lond., Emergency Report* No. 5, 1944.

S. WYATT, assisted by R. MARRIOTT, W. M. DAWSON, NORAH M. DAVIS, D. E. R. HUGHES and F. G. L. STOCK—
A study of certified sickness absence among women in industry. *Rep. Industr. Hlth Res. Bd, Lond.*, No. 86, 1945.
A study of women on war work in four factories. *Rep. Industr. Hlth Res. Bd, Lond.*, No. 88, 1945.

MEDICAL STATISTICS

Statistical Committee and Staff, London School of Hygiene and Tropical Medicine

Statistical Committee:—

Professor M. Greenwood, D.Sc., F.R.C.P., F.R.S. (*Chairman*).
L. Isserlis, D.Sc. (*Vice-Chairman*).

Professor of Medical Statistics:—

Professor A. Bradford Hill, D.Sc., Ph.D. (*appointed to Chair in 1945*).

Whole-time members of the Council's Staff:—

J. O. Irwin, D.Sc., Sc.D.
W. T. Russell, D.Sc. (*till August, 1943*).
E. Lewis-Faning, B.Sc., Ph.D.
W. J. Martin, D.Sc., Ph.D.
E. A. Cheeseman, B.Sc., Ph.D. (*on active service during the war*).

By arrangement between the Council and the Board of Management of the London School of Hygiene and Tropical Medicine, the Council's statistical staff have been accommodated since the opening of the School in its Department of Epidemiology and Vital Statistics. Throughout the war and for many years previously, the work was directed by Professor Major Greenwood, Chairman of the Council's Statistical Committee, as head of the Department. The Statistical Committee and staff also serve the Ministry of Health in the field of medical statistics.

In 1945, Professor Greenwood retired from his University Chair, and was succeeded as Professor of Medical Statistics by Dr. A. Bradford Hill. The Council's staff continue to work in the newly-named Department of Medical Statistics of the School under Professor Hill's direction.

Soon after the outbreak of war Professor Greenwood and his colleagues undertook for the Ministry of Home Security a study aimed at assessing the effects of bombing on the civilian population, and the protective value of shelters and other precautionary measures. When the enemy's large-scale bombing offensive began in 1940, Professor (then Dr.) Bradford Hill was attached on a full-time basis to the Ministry's Research and Experiments Department at Princes Risborough; he there directed the analyses of casualty rates and other relevant data. In spite of the difficulties inherent in the collection of such material, much useful information was obtained, bearing on such questions as the influence of the density of population upon the

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casualty rate (emphasising the wisdom of evacuation), the distribution of casualties between houses, shelters and elsewhere and, to some extent, the expected advantages to shelterers, the relative importance of particular causes of injury such as flying glass or bomb splinters, the number of casualties in large towns produced by an estimated weight of attack, and the casualty rates at different distances from the explosion.

When the bombing offensive had slackened in 1942, Dr. Hill left Princes Risborough and was seconded to the Medical Directorate of the Royal Air Force on a part-time basis, being appointed Civil Consultant in Medical Statistics. In this capacity he advised on numerous problems of great importance to the Service which were under study by the Flying Personnel Research Committee and its Sub-Committees (pp. 132-134). Among these were measurements of the function of night vision, psychological and other tests bearing on aircrew selection, psychiatric problems in operational flying and the work on air sickness. In addition to these special investigations, Dr. Hill gave statistical advice to many individual R.A.F. medical officers who were engaged in clinical and other investigations in the course of their duties. With Wing Commander G. O. Williams, R.A.F., he was concerned with the study of flying accidents and in the development of a return relating to the killed and injured, which was designed to throw light upon the specific nature and causes of the injuries produced in varying circumstances.

In relation to the work of the Council's Military Personnel Research Committee and its Sub-Committees, Dr. Hill gave much statistical help in the analysis of data on road accidents to Army vehicles (p. 140), and those arising from the trial of remedies for sea-sickness and air-sickness (pp. 138 and 258). Dr. Irwin's part in studies of the efficiency of men working under conditions simulating tropical climates has been mentioned on p. 260. With Dr. G. M. Morant, Dr. Hill was concerned in the analysis of measurements of armoured fighting vehicles personnel in relation to the design of tanks and their controls, which formed part of the research programme of the Council's Physiological Laboratory at Lulworth (p. 140); he also gave some advice on the statistical analyses of tank casualties (p. 146).

At the London School of Hygiene, Professor Greenwood continued to advise the Chief Medical Officer of the Ministry of Health on the epidemiology of some of the more important infectious diseases—including influenza, which had proved so grave a problem in 1918-19. He served as a member of the Council's Committee on Tuberculosis in Wartime (p. 69) and made various statistical analyses in relation to its work. In 1942 he was nominated to represent the Council on a committee appointed by the Board of Admiralty to inquire into the utilisation of naval medical statistics and to make recommendations. Acting also as Civilian Consultant in Medical Statistics to the Royal Navy, he gave advice to Surgeon Commander Fraser Roberts, R.N.V.R., on his analysis of deaths and invalidings during the war, and on many other subjects. Courses of instruction in the elementary principles of statistics were arranged for newly-commissioned Surgeon Lieutenants.

In relation to problems of the wartime diet, Dr. Lewis-Faning collaborated with Dr. E. H. M. Milligan, Medical Officer of Health for Glossop, in studies of the growth of infants in that town; the progress of these children appeared, in comparison with peacetime standards, to be very favourable.

Work by Dr. Lewis-Faning for the War Wounds Committee and its Anaerobes Sub-Committee has been mentioned on p. 30. Dr. Martin collaborated with Professor J. S. Young and Dr. A. H. Cruickshank, of Aberdeen, in examining, for the War Wounds Committee, the action of "heart extract powder" on wound healing (p. 43). Dr. Hill and Dr. Martin were responsible for the statistical analysis of the data collected by

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the Council's Committee on Haemoglobin Surveys (p. 419), and Dr. Hill undertook for the Blood Transfusion Research Committee a statistical analysis of the factors associated with fainting in blood donors (p. 190). Professor Greenwood and the statistical staff also took part in the work sponsored by the Jaundice Committee (p. 66).

Dr. Martin gave advice on the statistical aspects of an investigation into the effects of air disinfection by aerosols on the incidence of the common cold in a war factory, and made an analysis for the War Office of peptic ulcer records from a gastric diseases clinic; he also gave assistance to the Council's "Mass Radiography" Unit (p. 69). For the Medical Women's Federation, he analysed data bearing on the health of children in wartime day nurseries.

Other special wartime work in which members of the statistical staff collaborated included the investigation by Dr. Dora Colebrook and her colleagues of the value of artificial sunlight treatment in industry (p. 155), the survey by Dr. Russell Fraser and others of the incidence of neurosis in industry (p. 157), and analyses of the blood counts of luminising workers.

Miscellaneous Studies

In addition to his special activities mentioned above, Professor Greenwood undertook a study of the distribution of time intervals between successive cases of disease, and the development of statistical methods of using these as a criterion of infectivity. He also made an analysis of the casualties occurring in different wars.

Before leaving the Council's statistical staff, after nearly 30 years' service, to take up an appointment in the Department of Social Medicine at Oxford, Dr. Russell completed an important investigation of the epidemiology of diphtheria during the preceding 40 years. His report on the subject was issued by the Council in 1943. Among many interesting points, it demonstrated the high degree of success which had attended the wide-scale immunisation of children, particularly pre-school children, in New York and Toronto, thus providing cogent evidence in support of the diphtheria immunisation campaign promoted by the Ministry of Health in this country.

Dr. Russell collaborated with Professor Greenwood and Dr. Martin in an analysis of the mortality due to violence in England and Wales in the past 100 years, and with Dr. E. A. Aslett, Dr. P. D'Arcy Hart and Dr. Martin in a study of pneumokoniosis in relation to body build. He was also in charge of the statistical analysis of a large body of anthropometric data which had been collected by the military authorities before the war, under the Militia Act of 1939. On Dr. Russell's departure the supervision of this work was taken over by Dr. Martin and was approaching completion by the end of hostilities.

Dr. Irwin undertook much statistical research for the Accessory Food Factors Committee (p. 105) in connection with the estimation and standardisation of vitamin preparations and other problems. With Dr. T. F. Macrae, he published work on the estimation of riboflavin, and he assisted Dr. K. Coward in assessing the accuracy of the spectrophotometric method of estimating vitamin B_1. The results of the co-operative experiment, mentioned on p. 291, on the assay of vitamin E were analysed; they resulted in the establishment of an international standard for the vitamin (p. 243). Since 1935 three similar experiments have been carried out on the assay of vitamin A (p. 107); the first was a comparison of a halibut liver oil with the International Carotene Standard; in the second, the reference cod-liver oil of the U.S. Pharmacopoeia was compared with the International Standard; and in the third, the solid vitamin A β-naphthoate was similarly assayed. These experiments provided extensive data on the accuracy of vitamin A assays, and an

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analysis was made to determine the conversion factor for estimating the biological value from the results of the spectrophotometric assay; the accuracy of the spectrophotometric method was also assessed.

Other work by Dr. Irwin included an examination, in collaboration with Mr. H. Barkworth, of the validity of the presumptive coliform test, with special reference to the influence of the dimensions of the tubes and containers used; an analysis, on behalf of Dr. G. F. Petrie, of data on the stability of antipneumococcus serum; and the conclusion of his extensive statistical analysis of the data collected by Drs. C. C. and J. M. Twort on the carcinogenic properties of mineral oils.

Dr. Lewis-Faning's researches included some statistical studies of tuberculosis mortality, the analysis, with Dr. E. Fletcher, of about 1,000 cases of rheumatism, and a study of patients treated for burns in the Glasgow Royal Infirmary (p. 270) in relation to the features of the accident that had led to the injuries; he also shared with Dr. Hill in supervising the collection and analysis, for a sub-committee of the Council's Industrial Health Research Board, of records bearing on a possible relationship between the manufacture of an inorganic compound of arsenic and the incidence of cancer in the workers concerned.

Dr. Martin made a study of mortality from lobar pneumonia in London in relation to the introduction of treatment by the sulphonamides; he also demonstrated statistically the great improvement in the general well-being of London children over the past 30 years and the fall in child mortality in the country as a whole; in the field of epidemiology he examined the age incidence of diphtheria and the effects of family size upon it, the epidemic curve of measles, and the trends of infectious diseases since the introduction of sulphonamide chemotherapy. Other work included a study of the sex ratio at birth during the war years, a contrast of pneumonia mortality between men and women (suggesting that the habits and occupations of the male sex were an important factor), and a general discussion of the Registrar-General's social class mortality records.

Apart from their assistance to the Council, to the Ministry of Health and other official bodies, the statistical staff gave much expert advice during the war years, as hitherto, to independent research workers; a few instances of this kind have been recorded above, but many more could be mentioned.

H. Barkworth and J. O. Irwin—
The effect of the shape of container and size of gas tube in the presumptive coliform test. *J. Hyg., Camb.*, 1941, **41**, 180.
Comparative detection of coliform organisms in milk and water by the presumptive coliform test. With an appendix on the possible bactericidal effect of bile salt. *Ibid.*, 1943, **43**, 129.

H. Barkworth, J. O. Irwin and A. T. R. Mattick—
The plate count and methylene-blue reduction test applied to milk. *J. Dairy Res.*, 1941, **12**, 265.

A. Brown, E. Lewis-Faning and M. M. Whittet—
Some social aspects of burns in Glasgow. *Brit. med. J.*, 1945, **i**, 144.

K. H. Coward—
The accuracy of the spectrophotometric determination of vitamin B_1. With an appendix on the analysis of variance of the results, by J. O. Irwin. *Quart. J. Pharm.*, 1941, **14**, 329.

M. Greenwood—
Influenza; epidemiological aspects. *Practitioner*, 1944, **153**, 323.

M. Greenwood and E. Faning-Lewis—
Normal death-rate of the Navy. *Lancet*, 1944, **ii**, 574.

A. B. Hill—
Mortality from malignant disease. *Practitioner*, 1945, **155**, 27.

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J. O. IRWIN—

Discussion on E. G. Chambers and G. Udny Yule's Paper "Theory and observation in the investigation of accident causation". *J. R. Statist. Soc., Suppl.*, 1941, **7**, 101.

On the distribution of a weighted estimate of variance and on analysis variance in certain cases of unequal weighting. *J. R. Statist. Soc.*, 1942, **105**, 115.

The distribution of the logarithm of survival times when the true law is exponential. *J. Hyg., Camb.*, 1942, **42**, 328.

On the calculation of the error of biological assays. *Ibid.*, 1943, **43**, 121.

A table of the variance of $\sqrt{x}$ when x has a Poisson distribution. *J. R. Statist. Soc.*, 1943, **106**, 143.

The error of the biological assay of insulin by the mouse-convulsion test. *Quart. J. Pharm.*, 1943, **16**, 352.

A statistical examination of the accuracy of vitamin A assays. An analysis of three co-operative experiments designed to ascertain the value of the conversion factor for transforming spectrophotometric values into international units. *J. Hyg., Camb.*, 1944, **43**, 291.

J. O. IRWIN and J. C. D. HUTCHINSON—

Nutritive value of yeast protein. Addendum: Statistical examination of the experimental data. *Biochem. J.*, 1942, **36**, 477.

J. O. IRWIN and M. G. KENDALL—

Sampling moments of moments for a finite population. *Ann. Eugen., Camb.*, 1944, **12**, 138.

E. LEWIS-FANING—

A comparative study of the seasonal incidence of mortality in England and Wales and in the United States of America. *Spec. Rep. Ser. Med. Res. Coun., Lond.*, No. 239, 1940.

Respiratory tuberculosis: effect of the war on the length of the interval between notification and death. *Brit. med. J.*, 1943, **ii**, 684.

E. LEWIS-FANING and E. FLETCHER—

The chronic rheumatic diseases, with special reference to chronic arthritis. A survey based on 1,000 cases. *Post-Grad. med. J.*, 1945, **21**, 137.

E. LEWIS-FANING and M. MYERS—

Prognostic value of the blood sedimentation rate in pulmonary tuberculosis. *Brit. med. J.*, 1942, **ii**, 125,

T. F. MACRAE, J. C. D. HUTCHINSON, J. O. IRWIN, J. S. D. BACON and E. I. MCDOUGALL—

Comparative digestibility of wholemeal and white breads, and the effect of the degree of fineness of grinding on the former. *J. Hyg., Camb.*, 1942, **42**, 423.

W. J. MARTIN—

Mortality from lobar pneumonia in London. *Lancet*, 1940, **ii**, 161.

Mortality in childhood during 1920–38. *Brit med. J.*, 1945, **i**, 363.

Social class mortality. *Hum. Biol.*, 1945, **17**, 1.

E. H. M. MILLIGAN and E. LEWIS-FANING—

A study of the physical and nutritional condition of children in wartime. I-VI. *Med. Offr*, 1942, **67**, 77, 85, 93, 101, 109 and 117.

R. A. PETERS, R. H. S. THOMPSON, A. J. KING, D. I. WILLIAMS and C. S. NICOL—

The treatment of post-arsphenamine jaundice with sulphur-containing amino acids. With a statistical appendix by M. GREENWOOD and W. J. MARTIN. *Quart. J. Med.*, 1945, n.s. **14**, 35.

W. T. RUSSELL—

The epidemiology of diphtheria during the last forty years. *Spec. Rep. Ser. Med. Res. Coun., Lond.*, No. 247, 1943.

P. STOCKS and E. LEWIS-FANING—

Wartime incidence of and mortality from respiratory tuberculosis. *Brit. med. J.*, 1944, **i**, 581.

J. S. YOUNG, A. H. CRUICKSHANK and W. J. MARTIN—

An experimental study of the healing of wounds, with special reference to the action of heart extract powder (Doljanski). *J. Path. Bact.*, 1946, **58**, 63.

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OTHER MEMBERS OF THE COUNCIL'S EXTERNAL SCIENTIFIC STAFF (AND THEIR CO-WORKERS)

Diseases of Children

Queen Elizabeth Hospital for Children, London

Medical Research Council staff (part-time):—

Helen M. M. Mackay, M.D., F.R.C.P.

Dr. Mackay's investigations during the war years related mainly to problems of child nutrition. As differences of opinion existed as to the calorie requirements of infants during the neonatal period, she collected data regarding the food intake of normal breast-fed babies, and devised a scheme, based thereon, for calculating the calorie requirements during this period of both premature and full-term infants of varying birth weights. The mean rates of weight increase for premature infants fed according to this schedule proved to be as great as those for full-term, breast-fed infants.

In 1941, with Dr. Lucy Wills, Dr. R. H. Dobbs and Lady Bingham, Dr. Mackay examined the haemoglobin levels of groups of County Council school children, women medical students, and hospital nurses. There was evidence of lower haemoglobin levels in comparison with pre-war figures. By the following year, the haemoglobin level of the school children examined had improved. A group of children in day-nurseries in London were shown to be suffering from anaemia at least partly nutritional in origin, as judged by its improvement by both a better diet and iron therapy. An investigation by Dr. Mackay, with Dr. Dobbs and Lady Bingham, showed that bread made with the 85 per cent. extraction National flour was effective neither in its usual form, nor when the flour was fortified with extra iron, in raising the haemoglobin levels of anaemic children: the fact that this flour is an unsuitable vehicle for augmenting iron intake is presumably due to the formation of an insoluble iron salt by the action of phytic acid. In a further study, Dr. Mackay and her colleagues demonstrated that a mean rise of 6 per cent. in the haemoglobin levels of a group of nursery-school children, brought about by iron medication, caused a drop of 26 per cent. in their "absence rate", thus indicating that minor degrees of anaemia in young children, as in infants, lower resistance to infections, and that this can be raised by iron therapy. Another wartime survey, undertaken at a County Council school, showed that the mean haemoglobin levels of the children attending it were closely correlated with the economic status of the parents.

Other investigations undertaken by Dr. Mackay have been concerned with "Eumydrin" in the treatment of hypertrophic pyloric stenosis, the vitamin D requirements in rickets resistant to vitamin D, soya flour in infant feeding, and the use of protein hydrolysates in the feeding of premature infants.

R. H. Dobbs, H. M. M. Mackay and K. Bingham—
The haemoglobin level in municipal school children. *Brit. med. J.*, 1944, **ii**, 748.

H. M. M. Mackay—
Soya bean flour with dried milk: a cheap and efficient substitute for breast milk. *Arch. Dis. Childh.*, 1940, **15**, 1.

Eumydrin in the treatment of hypertrophic pyloric stenosis: an analysis of 40 consecutive cases. *Ibid.*, 1941, **16**, 1.

The calculation and prescribing of infants' feeds. (1) After the neonatal period. *Brit. med. J.*, 1941, **i**, 841. (2) The neonatal period. *Ibid.*, 1941, **i**, 888.

Calorie requirements of full-term and premature infants in the neonatal period. *Arch. Dis. Childh.*, 1941, **16**, 166.

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H. M. M. MACKAY—*(continued)*
Nutritional needs of infancy. *Proc. Nutrit. Soc.*, 1944, **2**, 69.
Nutrition of the premature infant in the first month of life. *Proc. R. Soc. Med.*, 1944-45, **38**, 51.
Congenital bilateral megalo-ureters with hydronephrosis: a remarkable family history. *Ibid.*, 1944-45, **38**, 567.

H. M. M. MACKAY, R. H. DOBBS and K. BINGHAM—
The effect of national bread, of iron medicated bread and of iron cooking utensils on the haemoglobin level of children in war time day nurseries. *Arch. Dis. Childh.*, 1945, **20**, 56.

H. M. M. MACKAY and Q. I. MAY—
Rickets resistant to vitamin D. *Proc. R. Soc. Med.*, 1944-45, **38**, 563.

H. M. M. MACKAY, L. WILLS and K. BINGHAM—
Economic status and the haemoglobin level of children of men in the fighting services and of civilians. *Brit. med. J.*, 1946, **i**, 711.

H. M. M. MACKAY, L. WILLS, R. H. DOBBS and K. BINGHAM—
Anaemia in women and children on war-time diets. *Lancet*, 1942, **ii**, 32.
Nutritional anaemia in children and women. *Proc. R. Soc. Med.*, 1942-43, **36**, 69.

L. WILLS, H. M. M. MACKAY, K. BINGHAM and R. H. DOBBS—
Anaemia in women and children on war-time diets. *J. Hyg., Camb.*, 1942, **42**, 505.

PATHOLOGY OF THE NERVOUS SYSTEM

The London Hospital; and the Nuffield Department of Surgery, Oxford

Medical Research Council staff:—

Miss Dorothy S. Russell, M.D., Sc.D., M.R.C.P.

Attached worker:—

Miss Diana J. K. Beck, M.B., F.R.C.S.

At the outbreak of war the neuropathological department of the Bernhard Baron Institute, the London Hospital, was transferred to Oxford, where Dr. Dorothy Russell had arranged, with the Council's approval, to continue work with Professor (now Sir Hugh) Cairns in the Nuffield Department of Surgery, and also to provide pathological service for the Military Hospital for Head Injuries at St. Hugh's College. In August, 1940, Dr. Rio Hortega left the Nuffield Department of Surgery and thereafter Dr. Russell became responsible also for the neuropathology in the department.

A series of investigations into the effects produced upon the tissues of the brain by direct application of a variety of antiseptic solutions was undertaken by Dr. Russell with Dr. Murray A. Falconer, and later with Miss Beck who had a grant from the Council. It was found that most of the antiseptics in current use were highly damaging to the brain; in particular, acriflavine, a potent member of the acridine series which gained favour in the treatment of wounds in the war of 1914-18, was very destructive. The closely allied and equally potent compound, proflavine, proved to be innocuous to brain tissue and was therefore recommended for practical use in the form of a buffered 1:1,000 solution at *p*H 6.2. Additional acridine antiseptics were tested later by the same technique, and, of these, 2:7 diamino-acridine hydrochloride and 5-amino-acridine hydrochloride proved to be similar to proflavine in their histological effects. Further tests in rabbits showed that proflavine, and the two other acridine compounds just mentioned, were highly damaging to brain, muscle and collagenous tissue when applied as powder to the freshly exposed normal tissues. On the other hand, various

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sulphonamides in powder form were found to be harmless to brain tissue (sulphathiazole, subsequently shown by other workers to be dangerous when applied to the brain, was not available when these tests were made). Mixtures of proflavine and sulphapyridine powders in varying concentrations were tried later and, as might be expected, proved to be damaging in proportion to the concentration of proflavine present; even mixtures containing only 0.5 per cent. of proflavine were not entirely innocuous. The sweeping success of penicillin in the treatment of bacterial infections in the later stages of the war led to a trial of the effects upon the brain of undiluted sodium penicillin and also of mixtures of calcium penicillin and sulphadimethylpyrimidine ("Sulphamezathine"). While sulphadimethylpyrimidine alone proved quite innocuous, the undiluted pencillin powder then available produced local necrosis and haemorrhage in the exposed brain, and mixtures of the two substances yielded intermediate effects.

The wide use of acrylic resins in dentistry and in plastic repairs of the jaw suggested that they might prove useful in the closure of defects in the skull. Histological study of a number of rabbit skulls into which a disc of acrylic resin had been grafted some months previously, showed that the disc became firmly encapsulated by fibrous tissue, the deep aspect of the capsule often being partly converted into lamellar bone. The growth of cells upon the actual surfaces of the disc showed that the acrylic resin had no cytotoxic properties.

Although infection of the brain, and in particular brain abscess, did not prove so frequent a complication of penetrating head injuries in the recent war as in that of 1914-18, owing to greatly improved preventive measures, it was considered at an early stage of the war that the experimental production and histological study of the stages of evolution of brain abscesses would be helpful. A successful technique was worked out, and it was found that encapsulation always began in the cortex and was completed last in the region of the lateral ventricle. The introduction of "Thorotrast" into the abscess cavity appeared to stimulate the development of the capsule about the dependent part of the cavity. No evidence was found in support of the widely expressed view that Gram-negative and anaerobic organisms inhibit the formation of a capsule.

In addition to these experimental studies, work was continued on a variety of neuropathological problems unconnected with the war: their nature is indicated by some of the publications listed below.

D. J. K. Beck and D. S. Russell—
Oligodendrogliomatosis of the cerebrospinal pathway. *Brain*, 1942, **65**, 352.

D. J. K. Beck, D. S. Russell, J. M. Small and M. P. Graham—
Implantation of acrylic-resin discs in rabbits' skulls. *Brit. J. Surg.*, 1945, **33**, 83.

W. E. Le Gros Clark and D. S. Russell—
Atrophy of the thalamus in a case of acquired hemiplegia associated with diffuse porencephaly and sclerosis of the left cerebral hemisphere. *J. Neurol. Psychiat.*, 1940, n.s. **3**, 123.

M. A. Falconer and D. S. Russell—
Experimental traumatic cerebral cysts in the rabbit. *J. Neurosurg.*, 1944, **1**, 182.

M. A. Falconer, A. M. McFarlan and D. S. Russell—
Experimental brain abscesses in the rabbit. *Brit. J. Surg.*, 1943, **30**, 245.

R. A. Henson and D. S. Russell—
Acute haemorrhagic leuco-encephalitis: report of a case. *J. Path. Bact.*, 1942 **54**, 227.

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C. F. FISCHMANN and D. S. RUSSELL—
The occurrence of intranuclear inclusions in cultures of foetal leptomeninges. *J. Path. Bact.*, 1940, **50**, 53.

D. HUNTER, R. R. BOMFORD and D. S. RUSSELL—
Poisoning by methyl mercury compounds. *Quart. J. Med.*, 1940, n.s. **9**, 193.

J. R. M. INNES, D. S. RUSSELL and A. J. WILSDON—
Familial cerebellar hypoplasia and degeneration in Hereford calves *J. Path. Bact.*, 1940, **50**, 455.

J. PENNYBACKER and D. S. RUSSELL—
Spontaneous ventricular rupture in hydrocephalus, with subtentorial cyst formation. *J. Neurol. Psychiat.*, 1943, n.s. **6**, 38.

R. A. ROWLANDS and S. L. SIMPSON with a pathological report by D. S. RUSSELL and H. M. TURNBULL—
The skeletal and other changes found in a case of suprasellar cyst of Rathke's pouch. *Brit. J. Surg.*, 1942, **29**, 304.

D. S. RUSSELL—
Contribution to discussion on "Fat embolism and the brain." *Proc. R. Soc. Med.*, 1941, **34**, 645.
Angiectasias y angiomas de cerebro y medula espinal. *Act. Espanol Neurol. Psiquiat.*, 1941, **2**, 133.
Contribution to discussion on "Venous thrombosis in the central nervous system." *Proc. R. Soc. Med.*, 1943–44, **37**, 390.
The pinealoma: its relationship to teratoma. *J. Path. Bact.*, 1944, **56**, 145.

D. S. RUSSELL and D. J. K. BECK—
Histological effects of sulphonamide-proflavine mixtures in the rabbit: some experimental observations. *Brit. med. J.*, 1944, **i**, 112.
Local action of penicillin and sulphamezathine, and a penicillin-sulphamezathine mixture on rabbit brain. *Ibid.*, 1945, **i**, 497.

D. S. RUSSELL and M. A. FALCONER—
Contribution to discussion on "The effect of antiseptics on wounds." *Proc. R. Soc. Med.*, 1940, **33**, 494.
Local effects of sulphonamides on the rabbit's brain. *Lancet*, 1940, **ii**, 100.
Antiseptics in brain wounds: an experimental study of the histological reaction of cerebral tissues to various antiseptic solutions. *Brit. J. Surg.*, 1941, **28**, 472.
Acridine antiseptics; further experiments on their local action. *Lancet*, 1943, **i**, 580.

D. S. RUSSELL and S. NEVIN—
Aneurysm of the great vein of Galen causing internal hydrocephalus. Report of two cases. *J. Path. Bact.*, 1940, **51**, 375.

BIOLOGICAL EFFECTS OF RADIATION

Strangeways Research Laboratory, Cambridge

Medical Research Council staff:—

F. G. Spear, M.D., D.M.R.E.

The work recorded here has formed part of the much wider programme of research carried out, with support from the Council, at the Strangeways Research Laboratory, under the Directorship of Dr. Honor B. Fell; reference to some other aspects of this programme is made on pp. 39, 40 and 371. Dr. Spear, the Deputy Director of the Laboratory, is a whole-time member of the Council's staff.

Dr. Spear had visited the United States on the Council's behalf, just before the war, to study the work of Lawrence and others, in California, on the medical uses of the cyclotron; since returning to Cambridge he has followed up the research done in America on the biological effects of neutrons; in these

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studies he collaborated with the late Dr. D. E. Lea. The work was done at the Cavendish Laboratory, Cambridge (where Professor J. D. Cockcroft kindly provided facilities for biological research with the cyclotron established there), and close co-operation was maintained with Dr. L. H. Gray and Dr. J. Read at the Mount Vernon Hospital, Northwood. The results show that while the general biological effects of neutron irradiation are in many ways similar to those of gamma- and X-rays in inhibiting cell division and causing cell degeneration, the time at which a particular response appears differs with the two types of radiation. Cell degeneration produced by neutron irradiation is more marked, occurs earlier and reaches a maximum more rapidly, than when X- or gamma- irradiation is used. Similar experiments made by Dr. K. Tansley and Dr. Spear with Dr. Gray, using alpha rays, produced for a given depression in cell division even more cell degeneration than that which follows neutron irradiation, and far more than anything so far obtained with single doses of X- or gamma-rays.

It is known that the destructive effects of gamma-rays can be increased if a given dose is divided. With amphibian tissue, Dr. A. Glücksmann and Dr. Spear showed that a second irradiation is most effective if delivered at a time when the effects of the first exposure are wearing off. The optimum spacing was found to be ten days. This result may be contrasted with earlier experiments with avian tissue cultures: in these, smaller doses of radiation were used, having a biological effect lasting only a few hours, and the optimum spacing was found to be 80 minutes.

Dr. Glücksmann and Dr. Spear, in collaboration with members of the Council's Radiotherapeutic Research Unit (p. 272), have been studying the response of malignant growths of the tongue and oral cavity to comparable doses of gamma- and X-radiation, by means of serial biopsies. The accessibility of such growths permits much greater precision in determining radiation dosage than is possible with cancer in other sites, though much useful information has been obtained also with regard to cancer of the cervix uteri. It has been found that a capacity for increased differentiation distinguishes tumours at these sites which respond well to radiation from those which fail to show any permanent benefit from radiotherapy.

A. Glücksmann and F. G. Spear—

The qualitative and quantitative histological examination of biopsy material from patients treated by radiation for carcinoma of the cervix uteri. *Brit. J. Radiol.*, 1945, n.s. **18**, 313.

L. H. Gray, J. C. Mottram, J. Read and F. G. Spear—

Some experiments upon the biological effects of fast neutrons. *Brit. J. Radiol.*, 1940, n.s. **13**, 371.

F. G. Spear—

The action of neutrons on bacteria. *Brit. J. Radiol.*, 1944, n.s. **17**, 348.

Medical uses of the cyclotron. *J. sci. Instr.*, 1945, **22**, 21. Reprinted in the 1945 Annual Report of the Smithsonian Institute, Washington, D.C.

F. G. Spear and A. Glücksmann—

The effect of gamma radiation on cells *in vivo*. Part III. Spaced radiation. *Brit. J. Radiol.*, 1941, n.s. **14**, 65.

Growth and new growth. *Proc. R. Soc. Med.*, 1941-42, **35**, 595.

F. G. Spear and K. Tansley—

The action of neutrons on the developing rat retina. *Brit. J. Radiol.*, 1944, n.s. **17**, 374.

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Chemotherapy

Liverpool School of Tropical Medicine

Medical Research Council staff:—

(i) J. D. Fulton, M.B., Ph.D., D.T.M.

(ii) E. M. Lourie, M.B., D.P.H., D.T.M. & H. (until *1944*).

(i) Dr. J. D. Fulton, who since 1938 had held a Leverhulme Research Fellowship (p. 58), became a member of the Council's scientific staff in 1941. In October, 1939, he was seconded to the Liverpool School of Tropical Medicine to supervise the maintenance of various strains of parasites, including those of malaria, trypanosomiasis, piroplasmosis and kala-azar, and also to carry out tests of new chemotherapeutic agents.

Early in the war Dr. Fulton investigated the actions of mepacrine and pamaquin, the British equivalents of the German antimalarials "Atebrin" and "Plasmochin". The British samples compared favourably in therapeutic effect and toxicity with their German prototypes. During the tests with pamaquin on monkeys infected with *Plasmodium knowlesi*, it was found that the parasites had developed resistance to the drug. In one series of experiments, during serial passage of *P. knowlesi* in monkeys, it was clearly demonstrated that the change occurred in the infecting organism, and the results were later confirmed. On the other hand, it was not found possible to render *P. gallinaceum* in fowls similarly resistant to pamaquin, and this failure was attributed to the fact that in fowls there is a well recognised exoerythrocytic stage of the parasite.

The malarial pigment present in the red blood cells of monkeys infected with *P. knowlesi* and in those of fowls infected with *P. gallinaceum* was shown by spectroscopic and other methods to be indistinguishable from haematin.

An investigation was made of the oedema which occurred in mice infected with *Trypanosoma cruzi*; it was shown that in them the swelling was not associated with lesions of the thyroid gland, in contradistinction to Chagas' contention that such swelling in human cases is myxoedematous. Claims had been made in Germany that the product Bayer 7602 Ac. was active against *T. cruzi* in Chagas' disease; a British equivalent was tested and proved to be identical with Bayer 7602 Ac., but neither specimen could eradicate *T. cruzi* infections in mice.

The diamidine series of drugs, which had already proved its usefulness in a number of protozoal infections, was further investigated. Stilbamidine (4:4' diamidino stilbene), one of the most active members of the series, was not very effective against *T. congolense* infections, which in African cattle cause serious economic loss: its dimethyl derivative, however, proved highly effective against the infection in mice. Field trials of the dimethyl derivative resulted in a certain percentage of cures, but the toxicity of the drug was too great for general use. 2-hydroxy stilbamidine proved as active as stilbamidine in leishmaniasis of hamsters: in this disease, penicillin was shown to be inactive both *in vivo* and against the flagellate stage of the parasites *in vitro*.

Following information from Dr. R. Kirk, of the Sudan Medical Service, regarding certain toxic effects that had followed the use of old solutions of stilbamidine, it was shown that a photochemical reaction occurred, with increase in toxicity and loss of therapeutic activity, when stilbamidine solutions were exposed to light. Other members of the diamidine series possessing an unsaturated linkage were also found to suffer photochemical change

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under the same conditions. The discolouration of solid stilbamidine on exposure to light was, by contrast, of little practical significance. It was therefore recommended that solutions should be freshly prepared just before use.

The blood levels of stilbamidine in mice were estimated by spectroscopic methods after administration of the drug by four different routes. It was found that the drug disappeared rapidly from the circulation after being speedily absorbed. A comparison of the therapeutic results obtained when drugs of this and other series were administered to trypanosome-infected mice by the same four routes showed that the best therapeutic index in the case of diamidines resulted when the subcutaneous route of administration was used. In spite of their rapid disappearance from the blood of mice, diamidines were found to possess marked prophylactic activity against trypanosome inoculations, which persisted for some weeks. Other workers have demonstrated a similar protective effect in man against *T. gambiense,* a result which is of considerable practical importance. Studies were also made of the immunity in mice which follows the cure of certain trypanosome infections by drugs. This immunity was found to depend to some extent on the antigenic stability of the trypanosomes in question, and on the number of organisms used for reinoculation.

It is easy to produce drug-resistance in trypanosomes, especially to arsenicals, by repeated sub-curative dosage; such strains were examined for the stability of this resistance. The resistance of an atoxyl- and Bayer 205-fast strain had lasted unimpaired for 12½ and 3½ years respectively, whereas the same species of trypanosome had lost all resistance to diamidines in a period of 2½ years. *Babesia canis,* on the other hand, had retained its resistance to diamidines for 2½ years.

The glucose metabolism *in vitro* of *T. rhodesiense* was investigated, and the products, which consisted of various fatty acids, glycerol, ethyl alcohol and carbon dioxide, were isolated.

Many of the hamsters used in studies of experimental leishmaniasis were found to be suffering from scabies due to infection with a parasite of *Notoëdres* sp., which may sometimes infect man. Tetra-ethylthiuram-monosulphide was found to be very effective in freeing them from parasites. The results of the treatment were communicated to Professor R. M. Gordon, who confirmed them and applied them to the treatment of human scabies. "Tetmosol", an emulsion of the substance just named, is now available as a commercial product.

These various investigations were carried out in collaboration with the authors named in the list of publications below.

(ii) At the outbreak of war Dr. E. M. Lourie was stationed in Sierra Leone in connection with work on sleeping sickness, and from 1940-42 he was formally seconded to the Sierra Leone Government in order to complete his studies in that country. On his return to the United Kingdom, Dr. Lourie worked in the department of the late Professor Warrington Yorke at the Liverpool School of Tropical Medicine. Professor Yorke died in 1943, and in the succeeding year Dr. Lourie ceased to be a member of the Council's scientific staff, on his appointment to the directorship of the newly-formed Warrington Yorke Department of Chemotherapy at Liverpool.

In Sierra Leone Dr. Lourie was engaged in the organisation of a campaign against a serious outbreak of sleeping sickness in the Kailahun District, and in the testing of certain of the diamidine series of drugs that had been

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shown in Liverpool to be active against experimental trypanosomiasis. As a result of the field trials, the following evaluation was made: (*a*) for early cases of sleeping sickness, both pentamidine and propamidine were as effective as tryparsamide, but stilbamidine was considerably less effective (probably on account of the photochemical decomposition of its solutions, a feature which was not appreciated at the time and which does not occur with pentamidine and propamidine); (*b*) for late cases, tryparsamide was far more effective than any of the three diamidines tested.

On returning to Liverpool in 1942, Dr. Lourie investigated the therapeutic effect of penicillin in protozoal and spirochaetal infections. No activity was found against trypanosomes or malaria parasites, but infections with *Spirochaeta recurrentis* and *Spirillum minus* proved to be susceptible, and these results suggested that penicillin might be effective also against human syphilis. However, it was not possible immediately to follow up this suggestion, since the supplies of penicillin available for clinical trial in Great Britain were at that time very limited; activity of the drug in human syphilis was accordingly first demonstrated in the United States. Subsequent studies on the mode of action of penicillin against spirochaetes in experimental animals and *in vitro* led to the adoption of penicillin courses suitable for outpatient administration in cases of early syphilis.

Dr. Lourie also investigated the possibility that mepacrine, like certain other non-arsenical acridine compounds, might produce resistance to arsenicals in trypanosomes. In view of the widespread and increasing use of mepacrine as an antimalarial in sleeping sickness areas, this matter was of great practical importance. Laboratory studies showed that there was probably no risk of the production of such resistance by mepacrine.

Other work included studies of the factors determining the efficacy of sleeping sickness drugs, the immunity of mice cured of trypanosome infections, and the action of diamidines against leishmania *in vitro*.

A. R. D. Adams, J. D. Fulton and W. H. Lumsden—

A comparison of the biological action of plasmoquine dihydrochloride (Bayer) and pamaquin dihydrochloride (I.C.I.). *Ann. trop. Med. Parasit.*, 1940, **34**, 223.

S. R. Christophers and J. D. Fulton—

The dissociation constants of plasmoquine. *Ann. trop. Med. Parasit.*, 1940, **34**, 1.

H. O. J. Collier, J. D. Fulton and J. R. M. Innes—

The oedema of mice infected with *Trypanosoma cruzi* and the accompanying pathological lesions. *Ann. trop. Med. Parasit.*, 1942, **36**, 137.

H. O. J. Collier and E. M. Lourie—

The action *in vitro* of diamidines and other compounds on *Leishmania donovani*. *Ann. trop. Med. Parasit.*, 1946, **40**, 88.

J. Devine and J. D. Fulton—

Observations on the nature of the malarial pigment present in infections of monkeys (*Macacus rhesus*) with *Plasmodium knowlesi*. *Ann. trop. Med. Parasit.*, 1941, **35**, 15.

The pigment formed by *Plasmodium gallinaceum* Brumpt, 1935, in the domestic fowl. *Ibid.*, 1942, **36**, 167.

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J. D. FULTON—

The course of *Plasmodium relictum* infection in canaries and the treatment of bird and monkey malaria with synthetic bases. *Ann. trop. Med. Parasit.*, 1940, **34**, 53.

Attempts to prepare in fowls a strain of *Plasmodium gallinaceum* resistant to plasmoquine. *Ibid.*, 1942, **36**, 75.

Studies in chemotherapy. 33. Toxicity and therapeutic action of certain aromatic diamidines after exposure to light. *Ibid.*, 1943, **37**, 48.

The treatment of Notoëdres infections in golden hamsters (*Cricetus auratus*) with dimethyl diphenylene disulphide (Mitigal) and tetra ethylthiuram monosulphide. *Vet. Rec.*, 1943, **55**, 219.

A comparison of the biological action of Bayer 7602 (AC) and the corresponding I.C.I. synthetic product. *Ann. trop. Med. Parasit.*, 1943, **37**, 164.

The prophylactic action of various aromatic diamidines in trypanosomiases of mice. *Ibid.*, 1944, **38**, 78.

The therapeutic action of some newer aromatic diamidines on *Leishmania donovani* infections of golden hamsters (*Cricetus auratus*). *Ibid.*, 1944, **38**, 147.

Penicillin in Leishmania infections. *Nature, Lond.*, 1945, **156**, 203.

J. D. FULTON and T. W. GOODWIN—

Studies on the estimation, adsorption and precipitation of stilbamidine. *J. Pharmacol.*, 1945, **84**, 34.

The effect of light on various aromatic diamidines in the solid state. *Ibid.*, 1945, **84**, 42.

J. D. FULTON and E. M. LOURIE—

The immunity of mice cured of trypanosome infections. *Ann. trop. Med. Parasit.*, 1946, **40**, 1.

J. D. FULTON and T. S. STEVENS—

The glucose metabolism *in vitro* of *Trypanosoma rhodesiense*. *Biochem. J.*, 1945, **39**, 317.

J. D. FULTON and W. YORKE—

Studies in chemotherapy. 27. Further observations on the stability of drug-resistance in Trypanosomes. *Ann. trop. Med. Parasit.*, 1941, **35**, 221; 28. Drug-resistance in Babesia infections. *Ibid.*, 1941, **35**, 229; 29. The development of plasmoquine-resistance in *Plasmodium knowlesi*. *Ibid.*, 1941, **35**, 233; 30. The trypanocidal action of additional aromatic diamidines. *Ibid.*, 1942, **36**, 131; 31. The increased toxicity of old solutions of stilbamidine. *Ibid.*, 1942, **36**, 134; 32. Further observations on plasmoquine resistance in *Plasmodium knowlesi*. *Ibid.*, 1943, **37**, 41; 34. Comparison of the results obtained by different methods of administration of drugs in trypanosomal infections of mice. *Ibid.*, 1943, **37**, 80; 36. The therapeutic action of various compounds in mice infected with *Trypanosoma congolense*. *Ibid.*, 1943, **37**, 152.

E. M. LOURIE—

Treatment of sleeping sickness in Sierra Leone. *Ann. trop. Med. Parasit.*, 1942, **36**, 113.

The blood-brain barrier and cerebrospinal fluid, in relation to the efficacy of sleeping sickness drugs. *Trans. Faraday Soc.*, 1943, **39**, 340.

E. M. LOURIE and H. O. J. COLLIER—

The therapeutic action of penicillin on *Spirochaeta recurrentis* and *Spirillum minus* in mice. *Ann. trop. Med. Parasit.*, 1943, **37**, 200.

Unimpaired susceptibility of *Trypanosoma rhodesiense* to arsenicals after intensive treatment by mepacrine. *Ibid.*, 1943, **37**, 205.

E. M. LOURIE, H. O. J. COLLIER, A. Q. F. ROSS, R. B. NELSON and D. T. ROBINSON—

Ambulatory treatment of early syphilis with penicillin. Rationale, experimental basis, and preliminary results. *Lancet*, 1945, **ii**, 696.

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E. M. Lourie and W. Yorke—
Studies in chemotherapy: XXI.—The trypanocidal action of certain aromatic diamidines. *Ann. trop. Med. Parasit.*, 1939, **33**, 289.
Studies in chemotherapy: XXII.—The action of certain aromatic diamidines on *Babesia canis* infections of puppies. *Ibid.*, 1939, **33**, 305.

A. O. F. Ross, R. B. Nelson, E. M. Lourie and H. O. J. Collier—
Treatment of early syphilis with penicillin. *Lancet*, 1944, **ii**, 845.

J. Williamson and E. M. Lourie—
Therapeutic action of different penicillins on *Spirochaeta recurrentis* infections in mice. *Brit. med. J.*, 1946, **i**, 828.

INVESTIGATORS APPOINTED TEMPORARILY TO THE COUNCIL'S EXTERNAL SCIENTIFIC STAFF DURING THE WAR

In relation to the extensive programme of research on war problems which has been reviewed in the introductory sections of this Report, a number of temporary additions to the Council's research staff were made during the period covered. Many of these temporary members of the staff were attached to the National Institute for Medical Research, or to one or other of the Council's permanent or semipermanent external research units or establishments, and their work has already been noticed under the appropriate headings above. The list of temporary research staff given below includes workers whose studies have not been specified, or adequately covered, in the earlier sections; it also includes the names of the principal members of some *ad hoc* research teams whose studies have been briefly noticed in the introductory sections. For convenience of reference, the headings of the corresponding introductory sections are used here. It may be added that some of the workers originally appointed on a temporary basis have become members of the Council's permanent research staff since the end of the period under review.

II.—Wounds and Injuries

Emergency Hospital, East Grinstead :—
Dora C. Colebrook, M.D. (see also pp. 156 and 342) :
Problems of wound infection.

Hill End Emergency Hospital, St. Albans ; and other centres :—
E. T. C. Spooner, M.D. (see also pp. 37, 135, 166 and 191) :
Problems of wound infection.

Leavesden Emergency Hospital, Abbots Langley ; and other centres :—
Joyce Wright, D.M. (see also pp. 37, 130, 342 and 343) :
Problems of wound infection ; control of cross-infection in hospitals.

Emergency Hospital, Mill Hill ; and elsewhere :—
Joan M. Ross, M.D. (see also p. 41) :
Collection and study of pathological specimens of war injuries.

University and Radcliffe Infirmary, Oxford :—
J. M. Barnes, M.B. (see also pp. 44 and 52) :—
Treatment of burns ; problems of "crush injury".

Emergency Hospital, Winwick, Warrington, Lancs :—
J. Doupe, M.D., M.R.C.P. :
Effects and treatment of peripheral nerve injuries (for the Nerve Injuries Committee, p. 49).

J. M. Barnes—
CTAB : a new disinfectant and cleaning agent. *Lancet*, 1942, **i**, 531.
The treatment of burns. *Brit. med. J.*, 1943, **i**, 408.

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J. M. BARNES and R. J. ROSSITER—
Toxicity of tannic acid. *Lancet*, 1943, **ii**, 218.

J. M. BARNES and J. TRUETA—
Arterial spasm : an experimental study. *Brit. J. Surg.*, 1942, **30**, 74.

J. DOUPE—
Studies in denervation. A.—Methods. *J. Neurol. Psychiat.*, 1943, n.s. **6**, 94. B.—The circulation in denervated digits. *Ibid.*, 1943, n.s. **6**, 97. D.—The mechanism of axonal vasodilatation. *Ibid.*, 1943, n.s. **6**, 115. E.—Observations concerning adrenaline. *Ibid.*, 1943, n.s. **6**, 121. I.—The contractility and excitability of denervated muscle. *Ibid.*, 1943, n.s. **6**, 141.

J. DOUPE, R. BARNES and A. S. KERR—
Studies in denervation. H.—The effect of electrical stimulation on the circulation and recovery of denervated muscle. *J. Neurol. Psychiat.*, 1943, n.s. **6**, 136.

J. DOUPE and C. H. CULLEN—
Studies in denervation. C.—Inflammation and trophic ulcers in denervated areas. *J. Neurol. Psychiat.*, 1943, n.s. **6**, 112.

J. DOUPE, C. H. CULLEN and G. Q. CHANCE—
Post-traumatic pain and the causalgic syndrome. *J. Neurol. Neurosurg. Psychiat.*, 1944, n.s. **7**, 33.

J. DOUPE, C. H. CULLEN and L. J. MACAULAY—
Studies in denervation. F.—The circulation in the skin of the proximal parts of the limbs. *J. Neurol. Psychiat.*, 1943, n.s. **6**, 129.

J. DOUPE and M. E. SHARP—
Studies in denervation. G.—Sebaceous secretion. *J. Neurol. Psychiat.*, 1943, n.s. **6**, 133.

W. MCKISSOCK, J. WRIGHT and A. A. MILES—
The reduction of hospital infection of wounds : a controlled experiment. *Brit. med. J.*, 1941, **ii**, 375.

A. A. MILES, H. SCHWABACHER, A. C. CUNLIFFE, J. P. ROSS, E. T. C. SPOONER, R. S. PILCHER and J. WRIGHT—
Hospital infection of war wounds. *Brit. med. J.*, 1940, **ii**, 855 and 895.

E. T. C. SPOONER—
The bacteriology of air-raid wounds examined within forty-eight hours of infliction. *Brit. med. J.*, 1941, **ii**, 477.
Observations on ' hospital infection ' in a plastic surgery ward. *J. Hyg., Camb.*, 1941, **41**, 320.

M. VAN DEN ENDE and E. T. C. SPOONER—
Reduction of dust-borne bacteria in a ward by treating floor and bedclothes. *Lancet*, 1941, **i**, 751.

III.—War Diseases

S.E. Asia Command :—
K. Mellanby, Ph.D. (see pp. 65 and 72) :
H. C. Browning, Ph.D. :
Work on scrub typhus.

Rothamsted Experimental Station, Harpenden :—
W. S. Richards, D.Phil. :
Biology of British species of *Trombicula* mite.

London Hospital and Cambridge University :—
C. Wilson, D.M. (*part-time*) :
Work on jaundice (see pp. 66 and 176).

Royal Hospital, Sheffield, and Radcliffe Infirmary, Oxford :—
Frances V. Gardner, B.Sc., M.D., M.R.C.P. :
Jaundice and rheumatoid arthritis (see p. 67).

C. WILSON, M. R. POLLOCK and A. D. HARRIS—
Therapeutic trial of methionine in infective hepatitis. *Brit. med. J.*, 1945, **i**, 399.

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V.—Nutrition in Wartime

London :—

Marjorie H. Craig :
Feeding of industrial workers (see p. 101).

University College Hospital, London ; and other centres :—

Joyce Wright, D.M. :
Bacteriological problems relating to the conservation of human milk (see p. 130).

VI.—Personnel Research

University of Cambridge and R.A.F. Physiological Laboratory, Farnborough :—

E. A. G. Goldie, M.B.
Measurements of oxygen saturation of the blood, and other physiological problems of aviation (for the Flying Personnel Research Committee, Air Ministry, p. 133).

M.R.C. Physiological Laboratory, Armoured Fighting Vehicle Training School, Lulworth, Dorset :—

O. M. Solandt, M.D., M.R.C.P. (1941–42)
Professor I. de Burgh Daly, M.D., F.R.S. (1942–45)
R. M. Mayon-White, M.B.
J. A. V. Bates, M.B.
J. A. B. Gray, M.R.C.S.
P. Hugh-Jones, M.B.
I. Leslie, B.Sc.
} see pp. 140–147.

London School of Hygiene and Tropical Medicine ; and field studies in Sierra Leone and Nigeria :—

J. S. Phillips, M.A., B.Sc., Ph.D. :
Work on insect repellents (for the Entomological Sub-Committee of the Military Personnel Research Committee, p. 138).

Admiralty Experimental Diving Unit :—

Helen Spurway, Ph.D. :
Work for the Royal Naval Personnel Research Committee.

E. A. G. Goldie—

A device for the continuous indication of oxygen saturation in the circulating blood in man. *J. sci. Instr.*, 1942, **19**, 23.

VII.—Health Research in Industry

Birmingham and elsewhere :—

Russell Fraser, M.D., M.R.C.P., D.P.M.
D. Elizabeth Bunbury, M.B., M.R.C.P., D.P.M.
Barbara Daniell, M.B., D.P.M.
M. Elizabeth Barling, M.A.
F. Estelle Waldron, B.A.
P. Mary Kemp, B.A.
Imogen Lee, M.A.
(with others)
} Incidence of neurosis among factory workers (see p. 157).

London and other centres :—

Dora C. Colebrook, M.D. (see also p. 340) :
Effect of "artificial sunlight" on the health of industrial and other workers (see p. 155–6).

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Middlesex Hospital, London :—

J. C. Jones, B.A.
M. J. Day, B.A.
} Assistance to Professor S. Russ, C.B.E., D.Sc., in measurements of the hazard of absorption of radio-active materials by workers in the luminising industry.

D. COLEBROOK—

Artificial sunlight treatment in industry : a report on the results of three trials—in an office, a factory and a coalmine. *Rep. Industr. Hlth Res. Bd, Lond.*, No. 89, 1946.

R. FRASER (with others)—

The incidence of neurosis among factory workers. *Rep. Industr. Hlth Res. Bd, Lond.*, No. 90, 1947.

VIII.—Special Emergency Services

University of Cambridge :—

R. I. N. Greaves, M.D. (*part-time*)
H. C. Gilson, B.A.
Margaret E. Mackay, B.Sc.
} Preservation of proteins by drying, especially plasma and serum for transfusion (see pp. 192–3).

N.W. London Blood Supply Depot, Slough :—

E. T. C. Spooner, M.D. (see pp. 37, 135, 166, 191 and 340) : Prevention of infection in blood transfusion.

R. I. N. GREAVES—

The freezing of human serum and plasma in Medical Research Council transfusion bottles, before drying by sublimation from the frozen state. *J. Hyg., Camb.*, 1942, **41**, 489.

Production of blood derivatives to meet war requirements in Great Britain. *J. Amer. Med. Ass.*, 1944, **124**, 76.

Centrifugal vacuum freezing. Its application to the drying of biological materials from the frozen state. *Nature, Lond.*, 1944, **153**, 485.

The preservation of proteins by drying : with special reference to the production of dried human serum and plasma for transfusion. *Spec. Rep. Ser. Med. Res. Coun., Lond.*, No. 258, 1946.

M. E. MACKAY—

The bacteriostatic effect of disinfectants in human serum and citrated plasma. *Brit. med. J.*, 1941, **i**, 747.

E. T. C. SPOONER and L. H. TURNBULL—

Notes on the use of autoclaves : with special reference to the sterilization of blood transfusion apparatus. *Bull. War Med.*, 1942, **2**, 345.

IX.—Miscellaneous Research and other Activities supported or assisted by the Council during the War.

North-Eastern (L.C.C.) Hospital, London ; and other centres :—

Joyce Wright, D.M. (see also pp. 37, 130, 340 and 342) : Control of cross-infection in hospitals ; sickness records of hospital nurses ; incidence and aetiology of middle ear suppuration in patients with measles.

J. WRIGHT—

Sickness records of nurses in a general hospital. *Brit. med. J.*, 1944, **i**, 585.

Cross-infection risks in the hospitalization of measles patients. *Ibid.*, 1945, **i**, 285.

J. WRIGHT, R. CRUICKSHANK and W. GUNN—

The control of dust-borne streptococcal infection in measles wards. *Brit. med. J.*, 1944, **i**, 611.

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XIV

RESEARCH WORK AIDED BY GRANTS

Investigations in Specific Subjects

In this chapter are recorded the research grants made by the Council to individual workers in aid of specific investigations during the period under review. As this period covers six years, it is not possible to do more than give a list of grant-holders, indicating in each case the type of grant received, and the main subject or subjects of research.

Many of the studies supported by grants were made in association with workers not themselves in receipt of grants, as will be seen from the list of references to published papers at the end of each section.

The effective periods of the grants varied widely, according to circumstances, ranging from one year or less to six years in all. (Grants for work already noticed in earlier Reports which continued for only a few months of the period under review are not recorded here, nor are grants which became effective only a few months before the end of the period; the latter will be mentioned in the next Report.)

Once again the Council are greatly indebted to the Rockefeller Foundation of New York for the provision of a special fund for the support of research in the fields of neurology, psychiatry and endocrinology. The grants made by the Council from this source, and from other funds previously placed at their disposal, are indicated accordingly.

WAR INJURIES

War Wounds (see pp. 28-43).

Captain G. Blum (now Blaine)—expenses: use of phosphatase for the promotion of bone repair after experimental fractures; plastic materials for the fixation of fractures. (Work carried out in the Department of Physiology, Leeds University, and under the supervision of Professor Samson Wright at the Middlesex Hospital Medical School, London, p. 39).

Professor C. H. Browning (University of Glasgow)—assistance by Dr. I. Lominski, and expenses: bacteriological studies of infected wounds, in relation to treatment and healing (for the Scottish War Wounds Committee, p. 42).

Professor D. F. Cappell (University of St. Andrews Medical School, Dundee)—assistance by Dr. H. E. Hutchison, and expenses: absorption of toxins from wounds; protective effect of granulation tissue.

Dr. R. A. Christianson (Strangeways Research Laboratory, Cambridge)—expenses: experimental studies of wound and tissue healing.

Professor J. Cruickshank, Professor J. S. Young and Professor W. C. Wilson (University of Aberdeen)—expenses: studies of wound infection and wound healing.

Dr. D. P. Cuthbertson and Dr. H. N. Munro (University of Glasgow)—assistance by Miss A. MacIvor and Miss M. I. Chalmers, and expenses: metabolic disturbances following injury; wound healing in relation to protein metabolism and intake.

Dr. J. N. Davidson (University of Aberdeen)—assistance by Dr. Charity Waymouth: chemical nature of tissue growth-promoting substances and their influence on wound healing.

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Professor A. D. Gardner and Professor Sir Howard Florey (University of Oxford)—assistance by the late Dr. Jean Orr-Ewing, and expenses: bacteriology of wounds treated in closed plaster (p. 34).

Sir Harold Gillies (Maxillo-Facial Unit, Park Prewett Hospital, Basingstoke)—expenses: follow-up studies of the results of plastic surgery for war injuries.

Dr. D. Herbert (University of Cambridge)—personal and expenses: chemistry of the toxins produced by haemolytic streptococci and gas-gangrene organisms (p. 309).

Major A. H. Hunt and Dr. B. Wolfe (London)—personal: assessment of the value of penicillin therapy for battle casualties (p. 36).

Dr. N. R. James (South Middlesex Emergency Hospital and West Middlesex County Hospital, London)—expenses: use of infiltration anaesthesia for air-raid and battle casualties (field studies by Major F. F. Rundle, p. 362).

Professor J. R. Learmonth (University of Edinburgh)—assistance by Dr. Rosamund M. I. Mackay, and expenses: clinical and experimental studies of the surgical treatment of wounds of blood vessels.

Dr. R. G. Macfarlane (Radcliffe Infirmary, Oxford)—personal: field studies of gas gangrene (p. 31), with special reference to the nature of the toxaemia (with Major J. D. MacLennan). (See also p. 354.)

Mr. B. C. Maybury and Dr. J. L. Feuchtwanger (Park Prewett Hospital, Basingstoke)—expenses: X-ray kymographic studies of the heart in cases of arterio-venous anastomosis.

Dr. P. B. Medawar (University of Oxford)—personal and expenses: studies of skin grafts, in relation to the problem of tissue transplantation immunity.

Professor A. A. Miles (University College Hospital Medical School, London)—assistance by Dr. E. M. Crook (see also p. 386), Miss Nancy Hayward and Mrs. E. M. Miles, and expenses: studies of wound infection, with special reference to anaerobic organisms (work carried out at the Central Pathological Laboratory, Watford, and the Birmingham Accident Hospital—see pp. 31 and 266).

Miss M. Mortell (Park Prewett Hospital, Basingstoke)—personal: bacteriological studies of wound infection (under the direction of Dr. L. Colebrook, p. 270).

Dr. W. E. van Heyningen (University of Cambridge)—personal and expenses: chemistry of gas-gangrene toxins in relation to toxoid production (pp. 32 and 308).

T. H. C. Barclay, D. P. Cuthbertson and A. Isaacs—
The influence of metabolic stimulants on wound healing; the influence of thyroid and 2-4-α dinitrophenol. *Quart. J. exp. Physiol.*, 1944, **32**, 309.

G Blum—
Phosphatase and the repair of fractures. *Lancet*, 1944, **ii**, 75.
Experimental observations of the use of absorbable and non-absorbable plastics in bone surgery. *Proc. R. Soc. Med.*, 1945, **38**, 169.

C. H. Browning—
The present status of aminoacridine compounds (flavines) as surface antiseptics. *Brit. med. J.*, 1943, **i**, 341.

D. P. Cuthbertson, G. B. Shaw and F. G. Young—
The anterior pituitary gland and protein metabolism. II. The influence of anterior pituitary extract on the metabolic response of the rat to injury. *J. Endocr.*, 1940, **2**, 468.
The anterior pituitary gland and protein metabolism. III. The influence of anterior pituitary extract on the rate of wound healing. *Ibid.*, 1940, **2**, 475.

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J. N. DAVIDSON and C. WAYMOUTH—
The effect of certain substances on the growth of tissues *in vitro*. *Biochem. J.*, 1942, **36**, iP.
Ribonucleic acids in animal tissues. *Nature, Lond.*, 1943, **152**, 47.
A factor in pancreatin which influences the growth of tissues *in vitro*. *J. Physiol.*, 1943–44, **102**, 8P.
The ribonucleic acid content of mammalian tissues. *Biochem. J.*, 1943, **37**, xiP.
Factors influencing the nucleoprotein content of fibroblasts growing *in vitro*. *Ibid.*, 1943, **37**, 271.
Liver ribonucleic acid. *Nature, Lond.*, 1944, **154**, 207.
The histochemical demonstration of ribonucleic acid in mammalian liver. *Proc. Roy. Soc. Edinb.*, B, 1944, **62**, 96.
Factors in pancreatin which influence the nucleoprotein content of fibroblasts growing *in vitro*. *Quart. J. exp. Physiol.*, 1944, **333**, 19.
Tissue nucleic acids. 1. Ribonucleic acids and nucleotides in embryonic and adult tissue. *Biochem. J.*, 1944, **38**, 39. 2. The isolation and properties of liver ribonucleic acid. *Ibid.*, 1944, **38**, 375. 3. The nucleic acid and nucleotide content of liver tissue. *Ibid.*, 1944, **38**, 379.
The nucleic acid and nucleotide content of tumours. *Brit. J. exp. Path.*, 1944, **25**, 164.
The nucleoprotein content of fibroblasts growing *in vitro*. 2. The effect of tissue extracts. *Biochem. J.*, 1945, **39**, 188.

T. GIBSON and P. B. MEDAWAR—
The fate of skin homografts in man. *J. Anat., Lond.*, 1943, **77**, 299.

N. J. HAYWARD—
The use of benzidine media for the identification of *Clostridium oedematiens*. *J. Path. Bact.*, 1942, **54**, 379.
The rapid identification of *Cl. welchii* by Nagler tests in plate cultures. *Ibid.*, 1943, **55**, 285.
The examination of wounds for clostridia. *Proc. Ass. Clin. Path.*, 1945, **1**, 5.

N. J. HAYWARD and J. A. B. GRAY—
Haemolysin tests for the rapid identification of *Cl. oedematiens* and *Cl. septicum*. *J. Path. Bact.*, 1946, **58**, 11.

N. J. HAYWARD and A. A. MILES—
Iron media for cultivation of anaerobic bacteria in air. *Lancet*, 1943, **i**, 645.

N. J. HAYWARD and R. PILCHER—
Anaerobic streptococcal myositis. *Lancet*, 1945, **ii**, 560.

J. W. HOWIE and J. CRUICKSHANK—
Effect of shock-producing substances on experimental anthrax infection in mice. *J. Path. Bact.*, 1947, **59**, 127.

H. E. HUTCHISON—
A method of producing experimental granulating wounds. *Lancet*, 1943, **ii**, 75.

N. R. JAMES—
Infiltrator for regional analgesia. *Lancet*, 1943, **i**, 738.
Machines for regional analgesia. *Proc. R. Soc. Med.*, 1943–44, **37**, 525.

I. LOMINSKI and G. R. THOMSON—
Relative sterility of the hands of certain metal workers. *Brit. J. industr. Med.*, 1944, **1**, 165.

R. G. MACFARLANE and J. D. MACLENNAN—
The toxaemia of gas-gangrene. *Lancet*, 1945, **ii**, 328.

J. D. MACLENNAN and R. G. MACFARLANE—
Toxin and antitoxin studies of gas-gangrene in man. *Lancet*, 1945, **ii**, 301.

P. B. MEDAWAR—
The behaviour and fate of skin autografts and skin homografts in rabbits. *J. Anat., Lond.*, 1944, **78**, 176.
A second study of the behaviour and fate of skin homografts in rabbits. *Ibid.*, 1945, **79**, 157.

A. A. MILES—
Epidemiology of wound infection. *Lancet*, 1944, **i**, 809.

A. A. MILES and E. M. MILES—
The fixation of foreign material in inflamed tissue, with especial reference to the action of *Cl. welchii* toxin and antitoxin. *Brit. J. exp. Path.*, 1943, **24**, 95.

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H. N. MUNRO and M. I. CHALMERS—
Fracture metabolism at different levels of protein intake. *Brit. J. exp. Path.*, 1945, **26**, 396.

J. ORR-EWING, J. C. SCOTT and A. D. GARDNER—
The bacteriological investigation of wounds treated by the closed-plaster method. *Brit. med. J.*, 1941, **i**, 877.

J. ORR-EWING, J. C. SCOTT, F. H. MASINA, J. TRUETA and A. D. GARDNER—
Local sulphanilamide treatment of fresh wounds in complete plasters. *Brit. J. Surg.*, 1944, **32**, 83.

W. E. VAN HEYNINGEN—
The biochemistry of the gas gangrene toxins. I. Estimation of the α toxin of *Cl. welchii*, type A. *Biochem. J.*, 1941, **35**, 1246.
The biochemistry of the gas gangrene toxins. 2. Partial purification of the toxins of *Cl. welchii*, type A. Separation of α and θ toxins. *Ibid.*, 1941, **35**, 1257.

J. S. YOUNG, A. H. CRUICKSHANK and W. J. MARTIN—
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Burns (see pp. 43–47)

Professor E. Finch and Mr. R. St. L. Brockman (Royal Infirmary, Sheffield)—expenses: treatment of burns.

Professor R. A. Peters (University of Oxford)—assistance by Dr. M. C. Manifold, Mr. E. J. Clark, Miss Ann Beloff and Mr. P. B. Croft, and expenses: experimental studies of burns and their metabolic effects (p. 45). (See also pp. 366 and 387).

A. BELOFF and R. A. PETERS—
The proteinase of skin. *J. Physiol.*, 1944–45, **103**, 2P.
Observations upon thermal burns: the influence of moderate temperature burns upon a proteinase of skin. *Ibid.*, 1944–45, **103**, 461.

E. J. CLARK, R. A. PETERS and R. J. ROSSITER—
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E. J. CLARK and R. J. ROSSITER—
Liver function in rabbits after injection of tannic acid. *Lancet*, 1943, **ii**, 222.
Metabolism of liver slices after burning. *Quart. J. exp. Physiol.*, 1944, **32**, 269.
Carbohydrate metabolism after burning. *Ibid.*, 1944, **32**, 279.

P. B. CROFT and R. A. PETERS—
Effect of methionine upon nitrogen losses in the urine following severe burns. *Nature, Lond.*, 1945, **155**, 175.
Nitrogen loss after thermal burns: effects of adding protein and methionine to diet of rats. *Lancet*, 1945, **i**, 266.

E. H. LEACH, R. A. PETERS and R. J. ROSSITER—
Experimental thermal burns, especially the moderate temperature burn. (A) Introduction and burning iron device; (B) Macroscopic and microscopic damage at moderate temperatures. *Quart. J. exp. Physiol.*, 1943, **32**, 67.

P. B. MEDAWAR—
Chemical coagulants in the treatment of burns. *Lancet*, 1942, **i**, 350.

J. M. ROBSON and A. B. WALLACE—
Use of a glycerin-sulphonamide paste ("Euglamide") in treatment of burns. *Brit. med. J.*, 1941, **i**, 469.

R. J. ROSSITER—
Controlled external pressure and oedema formation. (With a note by R. A. PETERS). *Lancet*, 1944, **i**, 9.

Head Injuries (see pp. 47–48)

Brigadier Sir Hugh Cairns (Radcliffe Infirmary, Oxford, and Military Hospital (Head Injuries), Oxford)—(*a*) assistance by Miss D. J. Dow: electro-encephalographic studies of head injuries; (*b*) expenses: follow-up studies of head injuries involving the frontal and paranasal sinuses.

Surgeon Captain M. Critchley (Royal Naval Hospital, Barrow Gurney)—expenses: follow-up studies of head injuries (and of peripheral nerve injuries) in Service personnel.

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Miss Diana J. K. Beck (Radcliffe Infirmary, Oxford)—personal*: effect of antiseptics and chemotherapeutic substances on brain tissue (p. 332); intracranial sinus thrombosis; cranial repair.

Dr. D. Denny-Brown (Military Hospital (Head Injuries), Oxford)—expenses: experimental concussion of the brain.

Dr. C. C. Evans (Hurstwood Park Hospital, Haywards Heath)—expenses: electro-encephalographic studies of brain injuries and disorders.

Professor S. Nevin (West Park Hospital, Epsom)—expenses*: pathology of brain injuries, including studies of blast effects on the nervous system.

Mr. W. McKissock (Leavesden Emergency Hospital, Abbots Langley)—expenses: effect of reconstituted dried human serum on the intracranial pressure.

Air Vice-Marshal Sir Charles Symonds (Military Hospital (Head Injuries), Oxford)—expenses: follow-up studies of head injuries in Service personnel.

Mr. W. Grey Walter (Burden Neurological Institute, Bristol)—expenses*: development and applications of a portable electro-encephalograph for the study of acute head injuries.

Wing Commander D. Williams (Military Hospital (Head Injuries), Oxford)—expenses: electro-encephalographic studies of brain injuries.

P. B. Ascroft—
Traumatic epilepsy after gunshot wounds of the head. *Brit. med. J.*, 1941, **i**, 739.

D. J. K. Beck—
Venous thrombosis in the central nervous system. *Proc. R. Soc. Med.*, 1943–44, **37**, 388.

D. J. K. Beck and D. S. Russell—
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Experiments on thrombosis of the superior longitudinal sinus. *J. Neurosurg.*, 1946, **3**, 337.

D. J. K. Beck, D. S. Russell, J. M. Small and M. P. Graham—
Implantation of acrylic-resin discs in rabbits' skulls. *Brit. J. Surg.*, 1945, **33**, 83.

H. Cairns—
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Head injuries in motor-cyclists. The importance of the crash helmet. *Brit. med. J.*, 1941, **ii**, 465.
Gunshot wounds of the head in the acute stage. *Ibid.*, 1944, **i**, 33.

H. Cairns and H. Holbourn—
Head injuries in motor-cyclists: with special reference to crash helmets. *Brit. med. J.*, 1943, **i**, 591.

C. A. Calvert and H. Cairns—
Injuries of the frontal and ethmoidal sinuses. *Proc. R. Soc. Med.*, 1941–42, **35**, 805.

H. Davies and M. A. Falconer—
Ventricular changes after closed head injury. *J. Neurol. Psychiat.*, 1943, n.s. **6**, 52.

D. Denny-Brown—
Delayed collapse after head injury. *Lancet*, 1941, **i**, 371.
The sequelae of war head injuries. *New Engl. J. Med.*, 1942, **227**, 771 and 813.

D. Denny-Brown and W. R. Russell—
Experimental cerebral concussion. *Brain*, 1941, **64**, 93.

R. S. Hooper, J. M. MacGregor and P. W. Nathan—
Explosive rage following head injury. *J. ment. Sci.*, 1945, **91**, 458.

M. Kremer—
Disorders of personality after head injury. *Proc. R. Soc. Med.*, 1943–44, **37**, 564.

A. D. Leigh—
Defects of smell after head injury. *Lancet*, 1943, **i**, 38.

W. Levin—
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* From a special fund provided by the Rockefeller Foundation.

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P. W. NATHAN and J. W. A. TURNER—
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P. W. NATHAN and C. W. M. WHITTY—
Measuring cerebrospinal fluid pressure. *Lancet*, 1942, **ii**, 154.

J. H. PATERSON—
Some observations on the cerebrospinal fluid in closed head injuries. *J. Neurol. Psychiat.*, 1943, n.s. **6**, 87.

W. R. REYNELL—
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D. S. RUSSELL and D. J. K. BECK—
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W. R. RUSSELL—
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Cerebral oedema. *Proc. R. Soc. Med.*, 1942, **35**, 528.
Transient disturbances following gunshot wounds of the head. *Brain*, 1945, **68**, 79.

C. P. SYMONDS—
Delayed traumatic intracerebral haemorrhage. *Brit. med. J.*, 1940, **i**, 1048.
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Differential diagnosis and treatment of post-contusional states. *Proc. R. Soc. Med.*, 1942, **35**, 601.

C. P. SYMONDS and W. R. RUSSELL—
Accidental head injuries: prognosis in service patients. *Lancet.*, 1943, **i**, 7.

J. W. A. TURNER—
Indirect injuries of the optic nerve. *Brain*, 1943, **66**, 140.
Facial palsy in closed head injuries. *Lancet*, 1944, **i**, 756.

W. G. WALTER and V. J. DOVEY—
Delimitation of subcortical tumours by direct electrography. *Lancet*, 1946, **i**, 5.

C. W. M. WHITTY—
On the so-called "laryngeal epilepsy." *Brain*, 1943, **66**, 43.

D. WILLIAMS—
The effect of cholin-like substances on the cerebral electrical discharges in epilepsy. *J. Neurol. Psychiat.*, 1941, n.s. **4**, 32.
The electro-encephalogram in acute head injuries. *Ibid.*, 1941, n.s. **4**, 107.
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D. WILLIAMS and D. DENNY-BROWN—
Cerebral electrical changes in experimental concussion. *Brain*, 1941, **64**, 223.

D. WILLIAMS and W. R. RUSSELL—
Action of eserine and prostigmin on epileptic cerebral discharges. *Lancet*, 1941, **i**, 476.

Nerve Injuries (see pp. 49-50).

Mr. M. Abercrombie and Dr. M. L. Johnson (University of Birmingham)—expenses: mechanism of Wallerian degeneration in peripheral nerves.

Dr. P. Bauwens (St. Thomas's Hospital, London)—personal and expenses: electrical studies of nerve injuries.

Mr. F. H. Bentley (University of Manchester)—expenses: experimental studies of nerve injuries, including problems of nerve grafting.

Dr. L. Guttman (Spinal Injuries Centre, Stoke Mandeville Hospital, Aylesbury)—personal* and expenses*: disturbances of the sweat mechanism in spinal injuries.

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Dr. W. Holmes (University of Oxford)—expenses: pathology of peripheral nerve lesions in relation to nerve suture and functional recovery (in association with Professor H. J. Seddon and Mr. J. Z. Young).

Professor G. Jefferson (University of Manchester and Peripheral Nerve Injury Centre, Winwick)—assistance by Dr E. Pollak: histopathology of nerve injuries.

Dr. R. L. Richards (Gogarburn Emergency Hospital, Edinburgh)—personal and expenses: skin temperature observations in health and disease, with particular reference to lesions of the nervous and vascular systems (under the direction of Professor J. R. Learmonth).

Professor H. J. Seddon (Wingfield-Morris Orthopaedic Hospital, Oxford)—expenses: rate of nerve regeneration in man after injury; treatment of peripheral nerve injuries and spinal injuries (partly with Dr. L. Guttman).

Dr. W. H. Sweet (Queen Elizabeth Hospital, Birmingham)—expenses: clinical, histological and electro-physiological studies of peripheral nerve injuries.

Dr. A. G. M. Weddell (University of Oxford)—personal and expenses: clinical and neuro-histological studies of sensation in man; problems of nerve degeneration and regeneration; electromyography. (Dr. Weddell also carried out an extensive programme of grant-aided work for the Royal Naval Personnel Research Committee, p. 149.)

Mr. J. Z. Young (University of Oxford)—assistance by Mr. D. Barker: recovery of proprioceptor function after nerve injury.

M. Abercrombie and M. L. Johnson—
Quantitative histology of Wallerian degeneration. I. Nuclear population in rabbit sciatic nerve. *J. Anat., Lond.*, 1946, **80**, 37.

P. Bauwens—
Electrodiagnostic interpretations in nerve lesions. *Proc. R. Soc. Med.*, 1943–44, **37**, 25.

F. H. Bentley and W. Schlapp—
Experiments on the blood supply of nerves. *J. Physiol.*, 1943–44, **102**, 62.
The effects of pressure on conduction in peripheral nerve. *Ibid.*, 1943–44, **102**, 72.

R. E. M. Bowden and E. Guttman—
Denervation and re-innervation of human voluntary muscle. *Brain*, 1944, **67**, 273.

M. A. Falconer and G. Weddell—
Costoclavicular compression of the subclavian artery and vein. *Lancet*, 1943, **ii**, 539.

B. Feinstein, R. E. Pattle and G. Weddell—
Metabolic factors affecting fibrillation in denervated muscle. *J. Neurol. Neurosurg. Psychiat.*, 1945, n.s. **8**, 1.

J. R. Learmonth, W. Blackwood and R. L. Richards—
Localised arterial thrombosis of indeterminate origin. *Edinb. med. J.*, 1944, **51**, 1.

J. R. Learmonth and R. L. Richards—
Note on the spinal origin of vasoconstrictor fibres to the arm in man. *Quart. J. exp. Physiol.*, 1943, **32**, 87.

R. L. Richards—
Vasomotor disturbances in the hand after injuries of peripheral nerves. *Edinb. med. J.*, 1943, **50**, 449.
Traumatic ulnar neuritis. The results of anterior transposition of the ulnar nerve. *Ibid.*, 1945, **52**, 14.
The assessment of sensory denervation after injuries of peripheral nerves. *Ibid.*, 1946, **53**, 110.
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H. J. Seddon, P. B. Medawar and H. Smith—
Rate of regeneration of peripheral nerves in man. *J. Physiol.*, 1943–44, **102**, 191.

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C. C. Ungley, G. D. Channell and R. L. Richards—
The immersion foot syndrome. *Brit. J. Surg.*, 1945, **33**, 17.

G. Weddell—
The multiple innervation of sensory spots in the skin. *J. Anat., Lond.*, 1940–41, **75**, 441.
The clinical significance of the pattern of cutaneous innervation. *Proc. R. Soc. Med.*, 1940–41, **34**, 776.
Axonal regeneration in cutaneous nerve plexuses. *J. Anat., Lond.*, 1942, **77**, 49.
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The anatomy of the thoracic outlet in relation to "irritation" and compression of nerve trunks. *Ibid.*, 1944–45, **38**, 601.

G. Weddell, B. Feinstein and R. E. Pattle—
The clinical application of electromyography. *Lancet*, 1943, **1**, 236.
The electrical activity of voluntary muscle in man under normal and pathological conditions. *Brain*, 1944, **67**, 178.

G. Weddell and P. Glees—
The early stages in the degeneration of cutaneous nerve fibres. *J. Anat., Lond.*, 1941, **76**, 65.

G. Weddell, L. Guttman and E. Guttman—
The local extension of nerve fibres into denervated areas of skin. *J. Neurol. Psychiat.*, 1941, n.s. **4**, 206.

G. Weddell and R. E. Pattle—
Demonstration of apparatus for recording muscle and nerve action potentials. *Proc. R. Soc. Med.*, 1941–42, **35**, 78.

Wound Shock and Related Problems (see. pp. 50-56)

Professor H. Barcroft (Queen's University, Belfast) and Professor O. G. Edholm (working at the British Postgraduate Medical School, London)—expenses: circulatory changes in post-haemorrhagic fainting—the "vaso-vagal syndrome" (with Professor J. McMichael—see below).

Dr. H. J. Brennan (Royal Infirmary, Manchester)—expenses: effect of haemorrhage on blood volume and red cell count, and its treatment with plasma transfusions.

Dr. E. G. L. Bywaters (British Postgraduate Medical School, London)—personal, assistance by Miss J. K. Stead, and expenses: clinical and experimental studies of crush injuries (pp. 52, 54 and 252).

Dr. R. B. Fisher (University of Oxford)—expenses: changes in cell-permeability following haemorrhage.

Professor Sir Howard Florey (University of Oxford)—assistance by Dr. E. P. Abraham: experimental studies of shock. (See also pp. 377 and 392.)

Professor H. N. Green (University of Sheffield)—assistance by Dr. T. Parkin and Mrs. M. Bielschowsky, and expenses (see also p. 392): experimental shock, with special reference to shock-producing factors in muscle (p. 54).

Mr. R. A. Jamieson (University and Western Infirmary, Glasgow)—personal: clinical and experimental studies of shock, with special reference to the blood sugar changes following haemorrhage (under the direction of Professor C. F. W. Illingworth).

Mr. A. W. Kay (University and Western Infirmary, Glasgow)—personal: venous pressure in shock and haemorrhage (under the direction of Professor C. F. W. Illingworth).

Dr. C. A. Keele (Middlesex Hospital Medical School, London)—expenses: effects of haemorrhage and shock on renal blood flow and function.

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Dr. (now Professor) J. McMichael (British Postgraduate Medical School, London)—assistance by Mr. D. K. Hill and Dr. J. Wallace, and expenses: effects of injury and haemorrhage on the blood circulation. (See also p. 354.)

The late Professor B. A. McSwiney (St. Thomas's Hospital Medical School, London)—assistance by Miss C. Mackenzie: influence of anaesthesia on the recovery of blood pressure following acute haemorrhage.

Professor W. C. Wilson (University of Aberdeen)—assistance by Mr. G. Kent Harrison, and expenses: circulatory changes following severe injury and during and after surgical operations; action of adrenal cortical extracts in wound shock. (See also pp. 53 and 344.)

Dr. W. S. Stanbury (University of Leeds)—expenses: blood plasma transfusion in traumatic shock.

Dr. Janet Vaughan (N.W. London Blood Supply Depot, Slough)—expenses: studies of pigment metabolism in relation to problems of blood transfusion.

E. P. Abraham, G. M. Brown, E. Chain, H. W. Florey, A. D. Gardner and A. G. Sanders—
Tissue autolysis and shock. *Quart. J. exp. Physiol.*, 1941, **31**, 79.

H. Barcroft and O. G. Edholm—
On the vasodilatation in human skeletal muscle during post-haemorrhagic fainting. *J. Physiol.*, 1945–46, **104**, 161.

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D. Beall, E. G. L. Bywaters, R. H. R. Belsey and J. A. R. Miles—
A case of crush injury with renal failure. *Brit. med. J.*, 1941, **i**, 432.

M. Bielschowsky and H. N. Green—
Shock-producing factor(s) from striated muscle. II. Fractionation, chemical properties and effective doses. *Lancet*, 1943, **ii**, 153.
Organic and inorganic pyrophosphates as shock-inducing agents. *Nature, Lond.*, 1944, **153**, 524.
Synthesis of adenosine triphosphate by an enzyme system from ischaemic muscle. *Ibid.*, 1945, **156**, 117.

M. Bielschowsky, H. N. Green and H. B. Stoner—
The effect of magnesium and calcium on the physiological properties of certain purine derivatives. *J. Physiol.*, 1945–46, **104**, 239.

H. J. Brennan—
Plasma transfusions in the treatment of haemorrhage. *Brit. med. J.*, 1940, **i**, 1047.

E. G. L. Bywaters—
Crushing injury. *Brit. med. J.*, 1942 **ii**, 643.
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Anatomical changes in the liver after trauma. *Clin. Sci.*, 1946, **6**, 19.

E. G. L. Bywaters and D. Beall—
Crush injuries with impairment of renal function. *Brit. med. J.*, 1941, **i**, 427.

E. G. L. Bywaters, A. C. Crooke and C. J. O. R. Morris—
Limb compression in the tube shelter disaster. *Lancet*, 1943, **ii**, 373.

E. G. L. Bywaters, G. E. Delory, C. Rimington and J. Smiles—
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E. G. L. Bywaters and J. H. Dible—
The renal lesion in traumatic anuria. *J. Path. Bact.*, 1942, **54**, 111.
Acute paralytic myohaemoglobinuria in man. *Ibid.*, 1943, **55**, 7.

E. G. L. Bywaters and G. Popjak—
Experimental crushing injury. *Surg. Gynec. Obstet.*, 1942, **75**, 612.

E. G. L. Bywaters and J. K. Stead—
The production of renal failure following injection of solutions containing myohaemoglobin. *Quart. J. exp. Physiol.*, 1944, **33**, 53
Thrombosis of the femoral artery with myohaemoglobinuria and low serum potassium concentration. *Clin. Sci.*, 1945, **5**, 195.

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C. B. B. Downman and C. C. Mackenzie—
Intracisternal injection of potassium phosphate. *Lancet*, 1943, **ii**, 471.

C. B. B. Downman, C. C. Mackenzie and B. A. McSwiney—
An optical method for recording peripheral blood pressures and pulse rates in unanaesthetized and in anaesthetized rabbits. *J. Physiol.*, 1944–45, **103**, 344.
The effects of acute haemorrhage on the peripheral blood pressure in unanaesthetized and in anaesthetized rabbits. *Ibid.*, 1944–45, **103**, 350.

E. M. Glaser and J. McMichael—
Effect of venesection on the capacity of the lungs. *Lancet*, 1940, **ii**, 230.

H. N. Green—
Shock-producing factor(s) from striated muscle. I. Isolation and biological properties. *Lancet*, 1943, **ii**, 147.

H. N. Green and H. B. Stoner—
The effect of adenosine triphosphate on a water diuresis in man. *J. Physiol.*, 1944, **103**, 28P.
Toxic extract from blood plasma of shocked animals. *Ibid.*, 1944, **103**, 30P.
Magnesium potentiation of adenosine triphosphate shock and other shock-inducing measures. *Brit. J. exp. Path.*, 1944, **25**, 150.

D. K. Hill—
Determination of blood-volume in shocked patients. *Lancet*, 1941, **i**, 177.

D. K. Hill, J. McMichael and E. P. Sharpey-Schafer—
Effects of serum and saline infusions. Quantitative studies in man. *Lancet*, 1940, **ii**, 774.

A. W. Kay—
Heat in the treatment of shock. *Brit. med. J.*, 1944, **i**, 40.

C. A. Keele and D. Slome—
Renal blood flow in experimental " crush syndrome ". *Brit. J. exp. Path.*, 1945, **26**, 151.
Adenosine triphosphate and renal blood flow. *J. Physiol.*, 1945, **104**, 26P.

J. McMichael—
Circulatory collapse and wound shock. *Edinb. med. J.*, 1941, **48**, 160.
The practical management of wound shock. *Brit. med. J.*, 1942, **ii**, 671.
Clinical aspects of shock. *J. Amer. Med. Ass.*, 1944, **124**, 275.

J. McMichael and E. P. Sharpey-Schafer—
Cardiac output in man by a direct Fick method. Effect of posture, venous pressure change, atropine, and adrenaline. *Brit. Heart J.*, 1944, **6**, 33.

J. McMichael, E. P. Sharpey-Schafer, P. L. Mollison and J. M. Vaughan—
Blood volume in chronic anaemia by a concentrated corpuscle-haemoglobin method. *Lancet*, 1943, **i**, 637.

E. P. Sharpey-Schafer—
Cardiac output in severe anaemia. *Clin. Sci.*, 1944, **5**, 125.
Transfusion and the anaemic heart. *Lancet*, 1945, **ii**, 296.

E. P. Sharpey-Schafer and J. Wallace—
Retention of injected serum in the circulation. *Ibid.*, 1942, **i**, 699.
Circulatory overloading following rapid intravenous injections. *Brit. med. J.*, 1942, **ii**, 304.

H. B. Stoner and H. N. Green—
Adenosine compounds and phosphates in the blood of shocked rabbits. *J. Path. Bact.*, 1944, **56**, 343.
The action of magnesium and calcium on the enzymic breakdown of certain adenine compounds. *Biochem. J.*, 1945, **39**, 474.
Further observations on the adenosine equivalent of the blood of rabbits following lethal forms of tissue injury. *J. Path. Bact.*, 1945, **57**, 337.
Experimental limb ischaemia in man, with especial reference to the role of adenosine triphosphate. *Clin. Sci.*, 1945, **5**, 159.

J. Wallace and E. P. Sharpey-Schafer —
Blood changes following controlled haemorrhage in man. *Lancet*, 1941, **ii**, 393.

W. C. Wilson—
State of men severely wounded in battle. *Lancet*, 1944, **i**, 587.

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CLINICAL MEDICINE

Dr. G. Bourne (St. Bartholomew's Hospital, London)—assistance by Dr. C. Evans, and expenses: causes and treatment of cardiac pain.

Professor J. Crighton Bramwell (University and Royal Infirmary, Manchester)—expenses: heart disease in recruits; penicillin treatment of subacute bacterial endocarditis; coarctation of the aorta; heart disease in pregnancy.

Professor L. S. P. Davidson (University and Royal Infirmary, Edinburgh)—assistance by Miss N. Gough, and expenses: disorders of the blood; rheumatic and nutritional diseases; diseases of the liver and biliary tract, and of the gastro-intestinal tract.

Dr. J. B. Donald (Royal Infirmary, Edinburgh)—personal: therapeutic use of protein hydrolysates (under the direction of Dr. C. P. Stewart).

Dr. Raymond Greene (Tindall House Emergency Hospital, Aylesbury)—expenses: studies of frostbite.

Professor H. P. Himsworth (University College Hospital Medical School, London)—expenses: clinical and experimental studies of liver disease.

Dr. R. D. Lawrence (King's College Hospital, London)—expenses: problems of diabetes and carbohydrate metabolism.

Dr. R. G. Macfarlane (Radcliffe Infirmary, Oxford)—assistance by Mrs. H. M. Jope, and expenses: methods of haemoglobin estimation (in relation to the Haemoglobin Survey, p. 102); blood disorders; therapeutic uses of blood products. (See also p. 345.)

Dr. (now Professor) J. McMichael (British Postgraduate Medical School, London)—assistance by Dr. Sheila V. Sherlock and Dr. Sheila Howarth, and expenses: problems of heart failure; studies of acute hepatitis and other diseases of the liver. (See also p. 352.)

Dr. Kate Maunsell (King's College Hospital, London, and Horton Emergency Hospital, Epsom)—personal: problems of allergy.

Dr. K. A. G. Mendelssohn (University of Oxford)—personal: application of physical methods to medical problems (under the supervision of Professor L. J. Witts).

The late Professor N. Morris (University and Stobhill Hospital, Glasgow)—expenses: disorders of calcium metabolism; disorders of carbohydrate metabolism, with special reference to the endocrines (aided by a supplementary expenses grant to Dr. A. Slessor): studies of circulatory and respiratory disease, digestive and blood disorders, and rheumatic disease.

Professor C. Bruce Perry (University of Bristol) and Professor K. D. Wilkinson (University of Birmingham)—expenses: sulphonamide chemoprophylaxis of acute rheumatism.

Dr. J. B. Rennie (University of Glasgow)—expenses: aetiology and treatment of acute infective hepatitis.

Dr. Margaret M. F. Robinson (St. Thomas's Hospital, London)—personal and expenses: control of failing lactation, with special reference to hormone therapy.

Dr. E. A. Schott (London School of Hygiene and Guy's Hospital, London)—assistance by Mrs. E. Hermes, and expenses: respiratory exchange during and after graded exercise.

Dr. S. L. Simpson (Willesden General Hospital, London)—expenses: studies of Addison's disease and Simmonds's disease.

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Dr. A. B. Taylor and Dr. W. T. Cooke (Birmingham United Hospital)—expenses: treatment of infective endocarditis with sulphapyridine and heparin.

Professor E. J. Wayne and Dr. A. Wilson (University of Sheffield)—expenses: mechanism of cyanosis; studies of Addison's disease, myasthenia gravis, and thyrotoxicosis; action of gorse extracts (with Professor G. R. Clemo, p. 375, and Professor Wilson Smith, p. 393).

Dr. J. F. Wilkinson (Royal Infirmary, Manchester)—assistance by Dr. F. X. Aylward and Mr. B. R. S. Mainwaring, and expenses: anti-anaemic principles in liver and stomach; blood transfusion and blood products; studies of blood diseases, porphyrin metabolism, lead intoxication, Addison's disease, hyperthyroidism, and arthritis.

Professor L. J. Witts (Radcliffe Infirmary, Oxford)—assistance by Miss S. D. Habgood and Mrs. S. Livingstone, and expenses: effect of toxic substances on the health of industrial workers (p. 159), and related problems of liver disease.

S. Alstead—
Expectorants in chronic bronchitis. *Edinb. med. J.*, 1940, **47**, 693.
Codeine in chronic bronchitis. *Glasg. med. J.*, 1940, **134**, 126.
Observations on Sahli's haemoglobinometer. *Post-Grad. med. J.*, 1940, **16**, 278.
Ammonium chloride and ammonium carbonate in chronic bronchitis. *Lancet*, 1941, **i**, 308.
Action of bismuth carbonate in gastric disease. *Ibid.*, 1941, **ii**, 420.
Charcoal blanket for deodorising discharges. *Ibid.*, 1942, **i**, 669.
Rate of blood-regeneration after haemorrhage. *Ibid.* 1943, **i**, 424.

W. F. Anderson—
Motility of the fasting stomach in health and disease. *Lancet*, 1943, **i**, 40.
The tonic action of strychnine. *Brit. med. J.*, 1944, **i**, 360.

W. F. Anderson and N. Morris—
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Clinical Trials of Penicillin

In relation to a scheme organised by the Penicillin Clinical Trials Committee (p. 87) the following grants were made for investigations into the clinical use and applications of penicillin:—

Dr. A. J. E. Rowe, Dr. J. Hardwicke, Dr. J. C. Lawrie, and Dr. H. J. L. Marriott (St. Mary's Hospital, London)—personal (under the direction of Professor Sir Alexander Fleming).

Dr. T. Parkes, Dr. C. H. Paine, Dr. J. W. Stewart and Dr. R. I. Meanock (Middlesex Hospital, London)—personal (under the direction of Mr. R. Vaughan Hudson).

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Dr. I. A. Roxburgh and Dr. T. A. Grimson (Hill End Hospital, St. Albans)—personal (under the direction of Professor R. V. Christie).

Lady Florey (Radcliffe Infirmary, Oxford)—personal and expenses. (Lady Florey also received personal and expenses grants for studies of penicillin therapy at the Central Middlesex County Hospital, London.)

Dr. E. C. Turton (Radcliffe Infirmary, Oxford)—personal (under the direction of Lieut.-Colonel S. J. Jeffreys).

Grants were also made to the following for bacteriological studies in relation to clinical trials of penicillin:—

Professor Sir Alexander Fleming (St. Mary's Hospital, London)—assistance by Dr. A. J. E. Rowe and Dr. C. H. Smith.

Professor L. P. Garrod (Hill End Hospital, St. Albans)—expenses.

Mr. D. C. Morley (University of Cambridge)—personal (under the direction of Dr. E. T. C. Spooner).

Dr. A. H. T. Robb-Smith (Radcliffe Infirmary, Oxford)—expenses.

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SURGERY

Mr. P. R. Allison (General Infirmary, Leeds)—expenses: aetiology and pathology of bronchiectasis; respiratory function in relation to thoracic operations and pulmonary disease.

Dr. A. Brown (Royal Infirmary, Edinburgh)—personal: relation of the thymus to creatine metabolism.

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Mr. J. T. Chesterman (City General Hospital, Sheffield)—expenses: evaluation of the factors in post-lobectomy expansion of the lungs; experimental studies of intestinal obstruction.

Mr. O. V. Lloyd-Davies (St. Mark's Hospital, London)—expenses: follow-up study of cases of cancer of the rectum and colon.

Mr. F. F. Rundle (Westminster Hospital Medical School, London)—expenses*: ocular changes in Graves's disease, and their relationship to hormonal disturbances.

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* From a special fund provided by the Rockefeller Foundation.

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OBSTETRICS AND GYNAECOLOGY

Mrs. R. Kapeller-Adler (Royal Infirmary, Edinburgh)—personal and expenses: histamine and histidine metabolism in normal and in toxaemic pregnancy.

Dr. C. Nicholson (Moreton-in-Marsh)—expenses: X-ray pelvimetry.

Mr. J. Stallworthy (Radcliffe Infirmary, Oxford)—expenses: effect of gonadotrophic hormones on ovulation.

Dr. A. M. Sutherland (Royal Maternity and Women's Hospital, Glasgow)—expenses: heart disease in pregnancy.

Mr. J. Wyatt (St. Thomas's Hospital Medical School—at Godalming)—expenses: treatment of ovarian cancer with testosterone.

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PAEDIATRICS

Dr. C. Elaine Field (University College Hospital, London, and Hospital for Sick Children, Great Ormond Street, London)—assistance by Dr. Elizabeth Lund and Dr. M. Ungar, and expenses: clinical and follow-up study of chronic chest diseases in children (in association with Dr. W. J. Pearson, Professor R. S. Pilcher and Dr. W. G. Wyllie).

Professor G. B. Fleming (Royal Hospital for Sick Children, Glasgow)—expenses: clinical and laboratory studies of disease in children.

Dr. G. Ormiston—personal: field studies of gastro-enteritis and other infections in infants and children.

Professor Sir Leonard Parsons (Children's Hospital, Birmingham)—assistance by Miss E. Tonks, Miss E. Finch, Miss E. M. Hickmans, Dr. Helen Humphreys and Dr. Phyllis Poyner-Wall, and expenses: clinical and laboratory studies of disease in children; value of protein hydrolysates for the treatment of premature and wasted infants (with Dr. Winifred Young—see below).

Dr. Elenora Simpson (James Mackenzie Institute for Clinical Research, St. Andrews)—personal and expenses: studies of infant mortality, and of child life and health, in St. Andrews.

Dr. Winifred F. Young (Children's Hospital, Birmingham, and University of Cambridge)—personal: kidney function in dehydrated infants (p. 275); protein requirements of sick and healthy infants. (Dr. Young also collaborated with Professor R. A. McCance, Dr. D. A. K. Black and others in a study of experimental dehydration in human volunteers, p. 100.)

A. G. V. Aldridge—
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R. A. McCance and W. F. Young—
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J. W. A. Mackenzie—
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NUTRITION

Dr. Harriette Chick and Dr. T. F. Macrae (Lister Institute, London)—assistance by Mr. J. S. D. Bacon, and expenses: nature of the vitamin B_2 complex; nutritive value of the potato, and of breads made from flour of different extraction rates. (Work carried out at Cambridge.)

Miss A. M. Copping (Lister Institute, London)—personal: biological estimation of the B vitamins in wheat flour, bread and other foodstuffs. (Carried out at Cambridge under the direction of Dr. Harriette Chick.)

Professor (now Sir Jack) Drummond (University College, London)—expenses: chemical studies of vitamins B_6 and E. (Carried out at the Middlesex Hospital, London, by arrangement with Professor E. C. Dodds.)

Dr. G. S. Fraenkel (Imperial College of Science, Biological Field Station, Slough)—assistance by Miss M. Blewett, and expenses: nutritional factors affecting insects.

Dr. S. K. Kon (National Institute for Research in Dairying, Reading)—assistance by Dr. E. H. Mawson, and expenses: composition of human milk in relation to the state of nutrition of mother and infant.

Professor W. H. Linnell (College of the Pharmaceutical Society, London)—assistance by Mr. E. P. Stevens: synthesis of the carotenoids.

Professor J. R. Marrack (London Hospital) and Dr. S. K. Kon (National Institute for Research in Dairying, Reading)—assistance by Mrs. F. M. V. Cowie, and expenses: visual dark adaptation in pregnant and lactating women.

Dr. K. Mellanby and Dr. Helen Mellanby (Sorby Research Institute, Sheffield)—personal and expenses (see also p. 395): effects of deprivation of vitamin A and vitamin C, and other nutritional studies in human volunteers (pp. 108 and 109). (In relation to these investigations a personal grant was also made to Dr. J. Pemberton.)

Professor R. A. Morton (University of Liverpool)—expenses: spectrographic and chemical studies of vitamins and other biological substances.

Dr. M. M. Murray (Bedford College, London)—assistance by Dr. G. E. Glock, and expenses (with Dr. Dagmar Wilson): problems of fluorosis; endemic goitre in relation to the mineral content of drinking water (p. 113). (See also p. 368.)

Professor R. A. Peters (University of Oxford)—assistance by Mr. H. W. Kinnersley, and expenses (see also pp. 347 and 387): studies of the vitamin B complex.

Dr. C. P. Stewart (Royal Infirmary, Edinburgh)—expenses: nutritional and other factors in dark adaptation; mode of occurrence of vitamin A in blood.

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Dr. Y. L. Wang (Dunn Nutritional Laboratory, Cambridge)—personal: estimation and standardisation of vitamins B_1 and B_2 (p. 296); studies of cellular and tissue metabolism (under the direction of Professor D. Keilin in the Molteno Institute of Biology at Cambridge).

The following grants were also made towards the cost of the Oxford Nutrition Survey directed by Dr. H. M. Sinclair: assistance by Dr. T. S. Rodgers, Dr. M. M. Whitty, Dr. M. K. Gregory, Miss C. M. Wood, Dr. C. L. Ievers, Mr. B. B. Lloyd and Mr. E. V. Quinn.

A. L. Bacharach, E. M. Cruickshank, K. M. Henry, S. K. Kon, J. A. Lovern, T. Moore and R. A. Morton—
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C. W. Carter, R. G. Macfarlane, J. R. P. O'Brien and A. H. T. Robb-Smith—
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The fate of tocopherols in the animal body. *Biochem. J.*, 1940, **34**, 34.

J. C. Drummond, R. L. Noble and M. D. Wright—
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L. M. Dzialoszynski, E. M. Mystkowski and C. P. Stewart—
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Deficiency of vitamin B_1 in man as determined by the blood cocarboxylase. *J. biol. Chem.*, 1940, **132**, 11.

K. M. Henry, S. K. Kon, T. W. Goodwin and R. A. Morton—
Vitamins A and D in dripping. *Lancet*, 1941, **i**, 311.

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The spectrographic determination of linoleic, linolenic and elacostearic acids. *Analyst*, 1945, **70**, 68.

F. H. Kemp, M. M. Murray and D. C. Wilson—
Spondylosis deformans in relation to fluorine and general nutrition. *Lancet*, 1942, **ii**, 93.

G. L. S. Konstam and H. M. Sinclair—
Cardiovascular disturbances caused by deficiency of vitamin B_1. *Brit. Heart J.*, 1940, **2**, 231.

H. A. Krebs and K. Mellanby—
Digestibility of national wheatmeal. *Lancet*, 1942, **i**, 319.
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B. B. Lloyd, E. B. Cheek, H. M. Sinclair and G. R. Webster—
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T. F. MACRAE, J. C. D. HUTCHINSON, J. O. IRWIN, J. S. D. BACON and E. I. MCDOUGALL—
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R. A. MORTON—
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Preparation of retinene *in vitro*. *Nature, Lond.*, 1944, **153**, 405.

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On the biological significance of the tocopherols (vitamin E). *Biochem. J.*, 1940, **34**, 32.

DENTAL DISEASE

Dr. M. M. Murray (Bedford College, London)—assistance by Dr. G. E. Glock, and expenses: development of dental enamel (p. 280); studies of dental fluorosis. (See also p. 366.)

Dr. J. Thewlis and others (National Physical Laboratory, Teddington)—expenses (by arrangement with the Department of Scientific and Industrial Research); X-ray studies of tooth structure (p. 280).

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Dental fluorosis and caries in London children. *Lancet*, 1942, **i**, 98.

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R. WHYTE—
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Diet and the calcified dental tissues. *Proc. Nutrit. Soc.*, 1945, **3**, 97.

NEUROLOGY

Dr. J. le Beau (St. Mary's Hospital, London)—personal: experimental and clinical studies of epilepsy.

The late Dr. Elizabeth C. Eaves (University of Sheffield)—expenses: pathology of epidemic encephalitis and other nervous diseases.

Dr. I. Mackenzie (Eastern District Hospital, Glasgow)—expenses: anatomy and pathology of the extra-pyramidal nervous system.

PSYCHOLOGY AND MENTAL DISORDERS

Dr. (now Professor) R. C. Browne (Radcliffe Infirmary, Oxford, and University Air Squadron, Cambridge)—personal: effect of drugs on the performance of aircraft pilots, including studies with the "Link" trainer (for the Flying Personnel Research Committee of the Air Ministry (p. 133), under the supervision of Professor L. J. Witts).

Professor F. L. Golla (Burden Neurological Institute, Bristol)—assistance by Mr. L. D. MacLeod*: effect of convulsants, and of experimental hyperthyroidism, on brain metabolism.

Dr. M. S. Jones and Dr. R. Scarisbrick (Mill Hill Emergency Hospital, London)—personal (Dr. Scarisbrick, under the direction of Dr. D. Richter), assistance by Miss V. J. Mellersh, and expenses: physiological and biochemical studies of the response to exercise in effort syndrome.

Dr. T. A. Munro and Dr. R. P. Cook (Royal Eastern Counties' Institution, Colchester)—personal* (Dr. Cook—see also pp. 377 and 386) and expenses*: studies of phenylketonuria.

Dr. J. H. Quastel—assistance by Dr. T. J. R. Macara*, and expenses*: biochemical studies of mental disorder, at the Royal Eastern Counties' Institution, Colchester. (See also p. 387.)

Dr. J. C. Raven (Royal Eastern Counties' Institution, Colchester, and Mill Hill Emergency Hospital, London)—personal*, assistance by Miss J. Walshaw*, and expenses*: standardisation, development and applications of intelligence tests.

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* From a special fund provided by the Rockefeller Foundation.

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Dr. E. Slater (Sutton Emergency Hospital, Surrey)—expenses: studies of mental disorder among twins.

Dr. A. M. Spencer (Banstead Mental Hospital, Sutton)—expenses: intravenous use of insulin in the treatment of schizophrenia.

R. C. Browne—
Amphetamine and caffeine citrate in anoxaemia. *Brit. med. J.*, 1946, **i**, 870.

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Matrix tests. *Ment. Hlth*, 1940, **1**, 10.
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In relation to investigations into the incidence and manifestations of non-pulmonary tuberculosis (p. 70), grants were made from the Dorothy Temple Cross Research Fellowships Fund to the following workers:—

Dr. P. W. Edwards (Cheshire Joint Sanatorium, Market Drayton) and Dr. J. A. Young (University of Cambridge)—expenses.

Professor J. W. S. Blacklock (Royal Infirmary, Glasgow)—assistance by Dr. Christine Buchanan, and expenses; Dr. Katherine J. Guthrie (Royal Hospital for Sick Children, Glasgow), Dr. H. J. R. Kirkpatrick (Royal Northern Infirmary, Inverness), Dr. Agnes R. Macgregor (Royal Hospital for Sick Children, Edinburgh), the late Dr. W. T. Munro (Glenlomond Sanatorium, Kinross), and Dr. J. Smith (City Hospital, Aberdeen)—expenses.

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CELL AND TISSUE GROWTH

Dr. Honor B. Fell and colleagues (Strangeways Research Laboratory, Cambridge)—expenses: physiological, pathological and experimental studies of wound healing; blood diseases; bacterial structure and reproduction; tumour growth; and radiobiology. (See also pp. 39, 40, 297 and 334).

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RADIOLOGY AND RADIOTHERAPY

Dr. C. B. Allsopp (University and Strangeways Research Laboratory, Cambridge)—personal and expenses: effect of radiations on substances of biological importance.

Mr. G. W. Blomfield (Royal Infirmary, Sheffield)—expenses: radium treatment of gynaecological disorders and diseases.

Dr. M. Donaldson and Dr. G. J. Neary (Mount Vernon Hospital, Northwood)—expenses: radium treatment of cancer of the uterus.

Sir Leonard Hill and Dr. H. J. Taylor (St. John Clinic, London)—expenses: effect on skin temperature of exposure to high and low sources of heat.

Dr. J. S. Mitchell (University of Cambridge)—personal and expenses: clinical and experimental studies of the radiotherapy of malignant tumours.

Dr. G. B. Stanford (London)—expenses: physical factors in indirect radiography.

Dr. G. B. B. M. Sutherland (University of Cambridge)—assistance by Mr. S. E. Darmon, and expenses: effects of infra-red radiations on tissues.

Clinical work with the radium belonging to H.M. Treasury which had been lent by the Council to various hospitals was virtually suspended, for security reasons, during the war; the steps taken by the Council and other bodies to augment the supply of radon, to compensate for the temporary restriction of radium treatment for cancer, have been described on p. 198. Some experimental work with National radium, lent to the Council by the Radium Commission, was carried out at a few research centres during the war years, and summaries of the reports on these investigations were published in the *British Journal of Radiology* (see below). The wartime work of the Council's radium beam therapy research group, and of the Radiotherapeutic Research Unit at the Hammersmith Hospital, has been described on pp. 272-274. Studies by Dr. F. G. Spear, of the Council's staff, and Dr. A. Glücksmann at the Strangeways Research Laboratory, Cambridge, have been noticed on pp. 334-335.

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CHEMOTHERAPY

Miscellaneous Studies

Mr. F. R. Bradbury and Mr. F. E. Crofts (University College, Nottingham)—expenses: preparation of acridine derivatives for testing as antiseptics.

Professor C. H. Browning (University of Glasgow)—assistance by Dr. Millicent H. S. Leslie, Dr. K. M. Calver and Dr. M. W. Leckie, and expenses: trypanocidal action of phenanthridine compounds. (See also p. 344.)

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Mr. N. Senior (London)—expenses: synthesis of sulphonamides and related compounds (under the supervision of Dr. W. H. Linnell).

The late Professor Warrington Yorke (Liverpool School of Tropical Medicine)—expenses: studies of trypanocidal compounds; problems of drug-resistance.

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Professor G. R. Clemo (King's College, Newcastle-on-Tyne)—expenses.

Professor J. W. Cook (University of Glasgow)—assistance by Dr. W. Graham. (See also p. 397.)

Dr. J. W. Cornforth and Dr. Rita H. Cornforth (University of Oxford)—personal and expenses. (Dr. and Mrs. Cornforth also collaborated with Sir Robert Robinson in work on penicillin synthesis—see p. 377.)

Mr. D. Ll. Hammick (University of Oxford)—expenses.

Dr. H. R. Ing (University of Oxford)—personal and expenses.

The late Lieut.-Col. S. P. James (University of Cambridge, and Horton Emergency Hospital, Epsom)—expenses.

Dr. W. O. Kermack (Royal College of Physicians' Laboratory, Edinburgh)—assistance by Mr. W. Webster and Miss B. E. Halcrow, and expenses. (See also p. 397.)

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Dr. F. E. King (University of Oxford)—assistance by Mr. R. J. S. Beer, and expenses. (See also p. 397.)

Dr. F. G. Mann (University of Cambridge)—assistance by Dr. N. B. Chapman and Mr. F. T. Naylor, and expenses. (See also p. 397.)

Professor Sir Robert Robinson (University of Oxford)—assistance by Mr. W. L. Glen and Miss J. M. Crum, and expenses. (See also pp. 377 and 397.)

Professor E. E. Turner (Bedford College, London)—assistance by Miss D. M. Hall.

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Penicillin Studies

Dr. D. M. Crowfoot (University of Oxford)—expenses: determination of the crystal and chemical structure of penicillin salts (p. 91).

Professor Sir Howard Florey (University of Oxford)—assistance by Dr. E. Chain, Dr. E. P. Abraham, Dr. Margaret A. Jennings and Dr. A. G. Sanders, and expenses: chemistry and therapeutic applications of penicillin and other antibiotic substances (p. 78 *et seq.*). (See also pp. 351 and 392.)

Professor Sir Ian Heilbron (Imperial College of Science, London)—assistance by Mr. J. A. Elvidge: penicillin synthesis (p. 93).

Professor Sir Robert Robinson (University of Oxford)—assistance by Mr. J. B. Jepson: penicillin synthesis (pp. 90-95). (See also pp. 376 and 397.)

Professor A. R. Todd (University of Manchester, and subsequently University of Cambridge)—assistance by Mr. J. Wardleworth, and Dr. B. A. Kilby, and expenses: penicillin synthesis. (See also pp. 387 and 397.)

Professor W. J. Tulloch and Dr. R. P. Cook (University College, Dundee)—assistance by Miss M. B. Brown: use of special media for penicillin production.

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Clinical uses of penicillin. *Brit. med. Bull.*, 1944, **2**, 9.

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General and local administration of penicillin. *Lancet*, 1943, **i**, 387.

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M. E. FLOREY, A. M. MCFARLAN and I. MANN—
Report of forty-eight cases of marginal blepharitis treated with penicillin. *Brit. J. Ophthal.*, 1945, **29**, 333.

M. E. FLOREY and R. E. O. WILLIAMS—
Hand infections treated with penicillin. *Lancet*, 1944, **i**, 73.

PHYSIOLOGY

Dr. A. E. Barclay (Nuffield Institute for Medical Research, Oxford)—expenses: cineradiographic studies of the foetal circulation.

Professor D. Burns (King's College, Newcastle-upon-Tyne)—expenses: studies of growing bone.

Dr. W. Burns (University of Aberdeen)—expenses: mechanisms of visceral sensation in amphibians and mammals.

Professor E. W. H. Cruickshank (University of Aberdeen)—expenses: studies of heart muscle and the blood circulation.

Professor F. Davies (University of Sheffield)—expenses: studies of the conducting system of the mammalian heart (with the late Professor D. M. Blair, of Glasgow University).

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Dr. S. E. Dicker (University of Bristol)—personal: effects of diet, posterior pituitary extracts, and diuretic drugs on kidney function.

Professor A. Hemingway (University of Leeds)—expenses: studies of artificial respiration, and of heart output in relation to muscular exercise.

Dr. G. N. Jenkins (St. Bartholomew's Hospital Medical College, London)—expenses: growth-promoting and anti-thyroid factors in liver tissue. (Work carried out in the Department of Zoology at Cambridge University.)

Dr. H. W. Kosterlitz (University of Aberdeen)—assistance by Miss R. M. Campbell, and expenses: metabolism of galactose; factors affecting the storage of protein in the liver.

Professor J. B. Leathes and Dr. C. L. G. Pratt (University of Oxford)—expenses: studies of blood coagulation.

Dr. J. M. Peterson (University College, Cardiff)—expenses: control of carbohydrate metabolism, with special reference to the function of the liver.

Professor H. S. Raper (University of Manchester)—assistance by Dr. G. K. McGowan and Mr. L. J. Zatman, and expenses: metabolism of secretion; toxicity of methyl alcohol.

Dr. J. Secker (King's College, Newcastle-on-Tyne)—expenses: hormonal control of sympathetic nerve transmission.

Professor S. Wright (Middlesex Hospital Medical School, London)—expenses: studies of phosphatase metabolism, with special reference to bone repair.

E. C. Amoroso, A. E. Barclay, K. J. Franklin and M. M. L. Prichard—
The bifurcation of the posterior caval channel in the eutherian foetal heart. *J. Anat., Lond.*, 1941–42, **76**, 240.

A. E. Barclay, J. Barcroft, D. H. Barron, K. J. Franklin and M. M. L. Prichard—
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The mechanism of closure of the ductus venosus. *Brit. J. Radiol.*, 1942, n.s. **15**, 66.
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J. Barcroft, J. A. Kennedy and M. F. Mason—
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D. M. Blair and F. Davies—
The conducting system in the human and in the calf heart. *J. Anat., Lond.*, 1939–40, **74**, 137.

D. M. Blair, F. Davies and E. T. B. Francis—
The conducting system of the marsupial heart. *J. Anat., Lond.*, 1942–43, **77**, 115.

W. Burns—
A pump of small internal volume. *J. Physiol.*, 1940–41, **99**, 102.
Economical development of long lengths of film or bromide paper. *J. Physiol.*, 1941–42, **100**, 13P.
Activity in visceral nerves. *Ibid.*, 1941–42, **100**, 11P.
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E. W. H. CRUICKSHANK, J. DUCKWORTH, H. W. KOSTERLITZ and G. M. WARNOCK—
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E. W. H. CRUICKSHANK and H. W. KOSTERLITZ—
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E. W. H. CRUICKSHANK and I. C. WHITFIELD—
The rate of mixing and disappearance of T.1824 (Evans' blue) injected into the circulation. *J. Physiol.*, 1944, **103**, 19P.
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F. DAVIES—
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F. DAVIES and E. T. B. FRANCIS—
The heart of the salamander (*Salamandra salamandra*, L.), with special reference to the conducting (connecting) system and its bearing on the phylogeny of the conducting systems of mammalian and avian hearts. *Philos. Trans.*, B, 1941, **231**, 99.

F. DAVIES, E. T. B. FRANCIS and L. B. WINTER—
The glycogen content of the frog's heart. *J. Physiol.*, 1941–42, **100**, 329.

F. DAVIES and E. T. B. FRANCIS—
Age changes in size of muscle fibres of the marsupial heart. *Nature, Lond.*, 1942, **149**, 410.
A graphical method of comparing the glycogen content of muscle fibres from various regions of the heart. *J. Anat., Lond.*, 1942–43, **77**, 115.
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F. DAVIES and H. E. HARDING—
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S. E. DICKER and H. HELLER—
The effect of high doses of vitamin A on the renal function of rats. *J. Physiol.*, 1945–46, **104**, 31P.

J. D. P. GRAHAM—
The air stream in the lung of the fowl. *J. Physiol.*, 1939–40, **97**, 133.
Respiratory reflexes in the fowl. *Ibid.*, 1939–40, **97**, 525.
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A. HEMINGWAY and E. NEIL—
An experimental study of different methods of artificial respiration. *Brit. med. J.*, 1944, **i**, 833.

H. W. KOSTERLITZ—
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H. W. KOSTERLITZ and R. M. CAMPBELL—
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H. W. KOSTERLITZ and I. D. CRAMB—
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H. W. KOSTERLITZ and C. M. RITCHIE—
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P. H. Silver and J. S. R. Golding—
Effects of sulphonamides on bone phosphatase. *Lancet*, 1945, **i**, 528.

E. W. Walls—
Specialized conducting tissue in the heart of the golden hamster (*Cricetus auratus*) *J. Anat., Lond.*, 1941–42, **76**, 359.
Specialized conducting tissue in the heart of the common hedgehog (*Erinaceus europaeus*). *Ibid.*, 1942–43, **77**, 294.

Physiology of Vision

Miss K. Tansley (Strangeways Research Laboratory, Cambridge, and University College, London)—personal and expenses: experimental studies of *retinitis pigmentosa* and other inherited retinal degenerations.

Mrs. W. M. Townley (University of Liverpool)—personal and expenses: studies of night-blindness (under the direction of Professor H. E. Roaf).

Dr. W. D. Wright (Imperial College of Science, London)—assistance by Mr. H. V. Walters and Miss M. Gilbert, and expenses: studies of colour perception; adaptation of the eye to light under different conditions of illumination.

M. Kerly and M. C. Bourne—
Glycolysis in retinal extracts. *Biochem. J.*, 1940, **34**, 563.

W. M. McKeon and W. D. Wright—
The characteristics of protanomalous vision. *Proc. Phys. Soc., Lond.*, 1940, **52**, 464.

H. V. Walters—
Some experiments on the trichromatic theory of vision. *Proc. Roy. Soc.*, B, 1942–43, **131**, 27.

H. V. Walters and W. D. Wright—
The spectral sensitivity of the fovea and extrafovea in the Purkinje range. *Proc. Roy. Soc.*, B, 1942–43, **131**, 340.

E. N. Willmer and W. D. Wright—
Colour sensitivity of the fovea centralis. *Nature, Lond.*, 1945, **156**, 119.

W. D. Wright—
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The sensitivity of the eye to small colour differences. *Proc. Phys. Soc., Lond.*, 1941, **53**, 93.
The fundamental principles of vision in very weak light. *Trans. Illum. Engng Soc., Lond.*, 1941, **6**, 23.
Spectral sensitivity of the retinal receptors. *Nature, Lond.*, 1943, **151**, 726.
The graphical representation of small colour differences. *J. Opt. Soc. Amer.*, 1943, **33**, 632.

Physiology of Hearing

Dr. A. W. G. Ewing and Mrs. I. R. Ewing (University of Manchester)—assistance by Dr. A. I. Goodman and Mr. H. B. Hood, and expenses: studies of hearing tests; speech defects and speech development in deaf children; diagnosis, treatment and training of children with defective hearing.

Dr. T. H. Turney (University of Liverpool)—personal and expenses: studies of hearing aids (under the direction of Professor E. W. Marchant).

A. W. G. Ewing—
Audiometric tests and the capacity to hear speech. *Proc. R. Soc. Med.*, 1939–40, **33**, 237.
Defective hearing and mental development. *Teacher of the Deaf*, 1941, **39**, 4.
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A. W. G. Ewing—
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A. W. G. Ewing and D. A. Gandine-Stanton—
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Notes on the training of babies who are deaf. Manchester University Press, 1942.
Deafness in infancy and early childhood. *J. Laryng.*, 1943, **58**, 137.
The growth of speech in the mind of a child born totally deaf. *Teacher of the Deaf*, 1943, **41**, 46.
Lipreading and hearing aids. Manchester University Press, 1944.

I. R. EWING and A. W. G. EWING—
The ascertainment of deafness in infancy and early childhood. *J. Laryng.*, 1944, **59**, 309.

E. W. MARCHANT and T. H. TURNEY—
A hearing aid for research and group use. *J. sci. Instr.*, 1940, **17**, 149.

Hormones

Dr. D. Beall (British Postgraduate Medical School, London)—expenses: isolation of oestrogens from the adrenal gland and the testis.

Professor E. C. Dodds (Middlesex Hospital, London)—assistance by Mr. F. W. Chattaway and Mr. S. W. Stroud, and expenses: chemistry of synthetic oestrogens; metabolism of oestrogens; posterior pituitary physiology; synthesis of morphine analogues.

Dr. C. H. Gray (King's College Hospital, London)—expenses (see also p. 386): ketogenic activity of pituitary extracts. (Work carried out at the Manor Institution, Epsom.)

Dr. A. W. Greenwood (University of Edinburgh)—expenses: biological assay of male hormone.

Professor L. Hogben, Dr. F. W. Landgrebe and Dr. H. Waring (University of Aberdeen)—expenses: studies of posterior pituitary hormones.

Dr. V. Korenchevsky (Lister Institute, London)—personal, and assistance by Miss K. Hall: experimental studies of the relationship between different hormones and between hormones and vitamins. (Work carried out in the Department of Zoology and the Nuffield Institute for Medical Research at Oxford University.)

Dr. W. H. Newton (University College, London)—expenses*: physiology of pregnancy, with special reference to the parts played by the pituitary gland and the placenta. (Work carried out partly at University College, Cardiff.)

Professor T. Nicol (King's College, London—expenses: fat distribution in the female reproductive tract, and its relationship to the ovarian hormones. (Work carried out at Glasgow University and at the Medical School, Birmingham.)

Dr. J. M. Robson (University of Edinburgh)—expenses: pharmacology of the sex hormones, with special reference to synthetic oestrogens.

Dr. E. F. Scowen (St. Bartholomew's Hospital, London)—assistance by Mrs. N. H. Callow*, Miss B. M. Crumley* and Mrs. A. M. Robinson*, and expenses*: urinary excretion of adreno-cortical substances (with Professor R. V. Christie); metabolism and therapeutic uses of the sex hormones, with special reference to progesterone.

Professor F. G. Young (St. Thomas's Hospital Medical School—at Godalming)—assistance by Miss M. P. Horlick, and expenses*: studies of anterior pituitary hormones, with special reference to diabetes and lactation; alloxan diabetes. (See also pp. 205 and 220.)

Dr. S. Zuckerman (University of Oxford)—expenses: experimental studies of sex hormones.

* From a special fund provided by the Rockefeller Foundation.

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D. Beall—
The isolation of oestrone from ox adrenals. *J. Endocr.*, 1940–41, **2**, 81.
The isolation of 2-oestradiol and oestrone from horse testes. *Biochem. J.*, 1940, **34**, 1293.

G. H. Bell—
The behaviour of the pregnant uterus of the guinea-pig. *J. Physiol.*, 1941–42, **100**, 263.
The movements of the unloaded uterus. *Ibid.*, 1940–41, **99**, 352.
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G. H. Bell and J. A. C. Knox—
The assay of oestrone in the guinea-pig. *J. Endocr.*, 1940–41, **2**, 399.

G. M. Bonser and J. M. Robson—
The effects of prolonged oestrogen administration upon male mice of various strains: development of testicular tumours in the Strong A strain. *J. Path. Bact.*, 1940, **51**, 9.

G. Bourne and S. Zuckerman—
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Changes in the adrenals in relation to the normal and artificial threshold oestrous cycle in the rat. *Ibid.*, 1940–41, **2**, 283.

N. R. Campbell, E. C. Dodds and W. Lawson—
The nature of the oestrogenic substances produced during the demethylation of anethole. *Proc. Roy. Soc.*, B, 1939–40, **128**, 253.

R. F. Dawson and J. M. Robson—
A technique for the perfusion of the foetal placental circulation. *Proc. Soc. Exp. Biol., N.Y.*, 1940, **43**, 758.

R. Deanesly and W. H. Newton—
The influence of the placenta on the corpus luteum of pregnancy in the mouse. *J. Endocr.*, 1940–41, **2**, 317.

E. C. Dodds—
Possibilities in the realm of synthetic estrogens. *Vitamins & Hormones*, 1945, **3**, 229.

E. C. Dodds, L. Golberg, E. I. Grünfeld, W. Lawson, C. M. Saffer, Jun., and R. Robinson—
Synthetic oestrogenic compounds related to stilbene and diphenylethane. II. *Proc. Roy. Soc.*, B, 1944–45, **132**, 83.

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E. C. Dodds, W. Lawson, S. A. Simpson and P. C. Williams—
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E. C. Dodds and R. Robinson—
Isomers of stilboestrol and its esters. *Nature, Lond.*, 1943, **151**, 305.

D. J. Dow—
The effect of desoxycorticosterone on the body-weight of frogs. *J. Endocr.*, 1940–41, **2**, 428.

D. Dow and S. Zuckerman—
The effect of vasopressin, sex hormones and adrenal cortical hormone on body-water in axolotls. *J. Endocr.*, 1939, **1**, 387.

F. M. P. Eckstein—
Unusually long pregnancy in a macaque. *J. Anat., Lond.*, 1944, **78**, 147.
The pisiform bone. *Nature, Lond.*, 1944, **154**, 182.

F. M. P. Eckstein and S. Zuckerman—
The effect of oestrogenic stimulation on the mangabey prostate. *J. Anat., Lond.*, 1944, **78**, 146.

H. T. Fawns, S. J. Folley and F. G. Young—
The galactopoietic action of pituitary extracts in lactating cows. 2. The response during the peak of lactation. *J. Endocr.*, 1944–46, **4**, 205.

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S. J. Folley, F. H. Malpress and F. G. Young—
Induction of lactation in goats and cows with synthetic oestrogens and anterior-pituitary extracts. *J. Endocr.*, 1944–46, **4**, 181.
The galactopoietic action of pituitary extracts in lactating cows. 3. Comparison of extracts of pituitary glands from different species. *Ibid.*, 1944–46, **4**, 212.

S. J. Folley, D. L. Stewart and F. G. Young—
Experiments on the use of tablets containing 50 per cent. hexoestrol for the artificial induction of lactation in the bovine. *J. Endocr.*, 1944–46, **4**, 43.

S. J. Folley and F. G. Young—
The galactopoietic action of pituitary extracts in lactating cows. 1. Dose-response relations and total yields during declining lactation. *J. Endocr.*, 1944–46, **4**, 194.

A. W. Greenwood and M. Burns—
The problem of the moult in the castrated brown leghorn fowl. *Quart. J. exp. Physiol.*, 1940, **30**, 163.

K. Hall—
Changes in the adrenals of gonadectomised male and female rats produced by prolonged injections of sex hormones. *J. Path. Bact.*, 1940, **51**, 75.

H. Hughes, L. L. Ware and F. G. Young—
Diabetogenic action of alloxan. *Lancet*, 1944, **i**, 148.

V. Korenchevsky—
Some effects of sex hormones on the secondary sex organs of castrated male rats. *J. Path. Bact.*, 1941, **52**, 268.
Sex hormones and the basophilic granulation of the liver cells in the rat. *Ibid.*, 1941, **52**, 341.
Natural relative hypoplasia of organs and the process of ageing. *Ibid.*, 1942, **54**, 13.

V. Korenchevsky and K. Hall—
Metaplasia and adenoma-like changes in the uterus of rats injected with sex hormones. *Nature, Lond.*, 1939, **144**, 1048.
Pathological changes in the sex organs after prolonged administration of sex hormones to female rats. *J. Path. Bact.*, 1940, **50**, 295.
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Correlation between sex hormones, thyroid hormones and desoxycorticosterone as judged by their effects on the weights of organs of gonadectomized rats. *Biochem. J.*, 1941, **35**, 726.

V. Korenchevsky, K. Hall, R. C. Burbank and J. Cohen—
Hepatotrophic and cardiotrophic properties of sex hormones. *Brit. med. J.*, 1941, **i**, 396.

V. Korenchevsky, K. Hall and B. Clapham—
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V. Korenchevsky and M. A. Ross—
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F. W. Landgrebe, E. Reid and H. Waring—
Further observations on the intermediate lobe pituitary hormone. *Quart. J. exp. Physiol.*, 1943–44, **32**, 121.

F. W. Landgrebe and L. Samson—
The Hogben pregnancy test, with a note on the breeding of Xenopus for the test. *J. Obstet. Gynaec.*, 1944, **51**, 133.

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W. Lawson, S. W. Stroud and P. C. Williams—
Oestrogen excretion in milk from oestrogenized cattle. *J. Endocr.*, 1944–46, **4**, 83.

W. H. Newton and K. C. Richardson—
Preparations showing the secretion of milk in hypophysectomized pregnant mice. *J. Endocr.*, 1940–41, **2**, 322.
Preparations showing the distribution of fatty substances and glycogen in the uterus of the ferret during the oestrous cycle. *J. Anat., Lond.*, 1938–39, **73**, 362.
The results of intravitam staining with trypan blue in the pseudo-pregnant uterus of the ferret. *Ibid.*, 1938–39, **73**, 363.

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A. G. Ogston, J. St. L. Philpot and S. Zuckerman—
Observations relating to the swelling of sexual skin in rhesus monkeys. *J. Endocr.*, 1939, **1**, 231.

J. M. Robson—
Prolongation of pregnancy in the hypophysectomized rabbit by progesterone and oestrogens. *J. Physiol.*, 1939–40, **97**, 517.
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J. M. Robson and J. Adler—
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J. M. Robson and M. Y. Ansari—
The fate of D.B.E. (*aadi*-(p-ethoxyphenyl)*β* A-phenyl bromoethylene) in the body. *J. Pharmacol.*, 1943, **79**, 340.

J. M. Robson and A. I. S. MacPherson—
Rate of disappearance of pituitary gonadotrophin from the blood of rabbits. *J. Pharmacol.*, 1940, **70**, 433.

J. M. Robson and A. Schönberg—
A new synthetic oestrogen with prolonged action when given orally. *Nature, Lond.*, 1942, **150**, 22.

M. A. Ross and V. Korenchevsky—
The thymus of the rat and sex hormones. *J. Path. Bact.*, 1941, **52**, 349.

A. Schönberg, J. M. Robson, W. Tadros and H. A. Fahim—
Synthetic oestrogens related to triphenylethylene. *J. Chem. Soc.*, 1940, p. 1327.

E. F. Scowen—
The metabolism and therapeutic use of progesterone. *Proc. R. Soc. Med.*, 1943–44, **37**, 677.

E. P. Sharpey-Schafer and S. Zuckerman—
The effect of oestrogenic stimulation on the human prostate at birth. *J. Endocr.*, 1940–41, **2**, 431.

S. W. Stroud—
The metabolism of the parent compounds of some of the simpler synthetic oestrogenic phenols. *J. Endocr.*, 1940–41, **2**, 55.
Evidence of demethylation in the animal body. *Nature, Lond.*, 1940, **146**, 166.

G. I. M. Swyer and S. Zuckerman—
The effect of denervation on the structure and hormonal responses of the monkey prostate. *J. Anat., Lond.*, 1940–41, **75**, 368.

F. G. Young—
"Growth" and the diabetogenic action of anterior pituitary preparations. II. Growth and experimental insulin-insensitive diabetes. *Brit. med. J.*, 1944, **ii**, 715.
Growth and diabetes in normal animals treated with pituitary (anterior lobe) diabetogenic extract. *Biochem. J.*, 1945, **39**, 515.

S. Zuckerman—
The histogenesis of tissues sensitive to oestrogens. *Biol. Rev.*, 1940, **15**, 231.
Periodic uterine bleeding in spayed rhesus monkeys injected daily with a constant threshold dose of oestrone. *J. Endocr.*, 1940–41, **2**, 263.
The effect of desoxycorticosterone on the endometrium of monkeys. *Ibid.*, 1940–41, **2**, 311.
The effect of previous on subsequent responses of rhesus monkeys to oestrogens. *Ibid.*, 1940–41, **2**, 438.

S. Zuckerman and J. R. Groome—
An experimental study of the morphogenesis of intersexuality. *J. Anat., Lond.*, 1939–40, **74**, 171.

S. Zuckerman and A. S. Parkes—
Observations on secondary sexual characters in monkeys. *J. Endocr.*, 1939, **1**, 430.

BIOCHEMISTRY

Dr. H. K. F. Blaschko (University of Oxford)—personal, and assistance by Mrs. Ruth Duthie: studies of enzymic systems in relation to the formation of amines and to the detoxication of drugs in the body.

Professor J. H. Burn (University of Oxford)—assistance by Mrs. Ruth Duthie, and expenses; pharmacological studies of mepacrine.

Professor H. J. Channon (University of Liverpool)—expenses: fat metabolism in the liver; metabolism of trinitrotoluene.

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Professor A. C. Chibnall (Imperial College of Science, London, and subsequently University of Cambridge)—assistance by Dr. G. R. Tristram, Mr. H. Gutfreund and Dr. F. Sanger, and expenses: chemical structure of insulin.

Dr. R. P. Cook (University College, Dundee)—expenses (see also pp. 369 and 377): nitrogen content of human plasma proteins.

Mr. T. B. B. Crawford (University of Edinburgh)—expenses: metabolism of organic arsenical compounds.

Dr. E. M. Crook (University of Cambridge)—personal and expenses: chemistry of *Proteus* antigens and of gas-gangrene toxins (under the supervision of Dr. N. W. Pirie, by arrangement with Professor A. A. Miles—see pp. 31 and 345).

Dr. G. S. Dawes (University of Oxford)—personal and expenses: pharmacological studies of new synthetic compounds (under the direction of Professor J. H. Burn).

Dr. C. H. Gray (King's College Hospital, London)—expenses (see also p. 382): pigment metabolism in jaundice. (Work carried out at the Manor Institution, Epsom.)

Dr. (now Professor) F. C. Happold (University of Leeds)—assistance by Miss M. Sandford, and expenses: nutritional requirements of *C. diphtheriae* and other studies of bacterial metabolism; microbiological assay of vitamins.

Dr. H. G. M. Henry and Dr. (now Professor) M. Stacey (University of Birmingham)—personal (Dr. Henry), assistance by Mr. M. G. Webb (Professor Stacey), and expenses: chemistry of bacterial nucleoproteins, with special reference to the Gram complex.

Dr. E. R. Holiday (London Hospital)—personal, assistance by Mr. E. M. Jope, and expenses: applications of absorption spectrophotometry to biochemical problems.

The late Professor Sir Frederick Hopkins (University of Cambridge)—assistance by Mr. E. J. Morgan: oxidation-reduction processes in living tissues: relationship of vitamins to growth.

Dr. R. A. Kekwick (Lister Institute, London)—expenses: electrophoretic and ultracentrifugal studies of serum proteins.

Dr. (now Professor) E. J. King (British Postgraduate Medical School, London)—assistance by Mr. A. L. Tarnoky and Dr. I. D. P. Wootton, and expenses: problems of haemoglobinometry (p. 102): estimation of antimalarial drugs (pp. 60 and 61). (See also pp. 31 and 392.)

Dr. A. Kleinzeller (University of Cambridge)—personal and expenses: fat metabolism and fat production in yeast (under the direction of Dr. Marjory Stephenson, p. 309).

Dr. (now Professor) H. A. Krebs (University of Sheffield)—assistance by Mrs. M. Bielschowsky and Miss L. Shephard, and expenses: intermediary metabolism of carbohydrates and fatty acids: nutritional studies in human volunteers (pp. 108 and 109); studies of industrial fluorosis. (See also p. 304.)

Professor G. F. Marrian (University of Edinburgh)—assistance by Dr. Nancy Gough, and expenses: chemistry of urinary steroids, with special reference to their excretion in cancer.

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Dr. A. Neuberger (University of Cambridge)—personal, and assistance by Mr. J. L. Crammer: composition of the nitrogenous constituents of the potato; chemistry of the anti-pernicious anaemia factor in liver. (See also pp. 205 and 221.)

Professor R. A. Peters (University of Oxford)—expenses: problems of brain chemistry. (See also pp. 347 and 366.)

Professor R. A. Peters and Mr. J. St. L. Philpot (University of Oxford)—personal (Mr. Philpot), and expenses: ultracentrifugal studies of new proteins and other substances.

Dr. J. H. Quastel (City Mental Hospital, Cardiff)—personal, assistance by Dr. P. J. G. Mann*, Dr. D. M. Webley* and Dr. J. J. Gordon, and expenses: problems of brain chemistry; effect of organic arsenical compounds on tissue proteins and enzyme systems. (See also p. 369.)

Dr. J. H. Schulman (University of Cambridge)—personal and expenses: physico-chemical properties of surface films in relation to the study of biological systems.

Mrs. E. Stedman (University of Edinburgh)—personal: chemistry of cell nuclei (with Dr. E. Stedman).

Professor A. R. Todd (University of Cambridge)—assistance by Mr. J. Baddiley: studies of codecarboxylase (with Dr. E. F. Gale, p. 308) and purine nucleotides. (Mr. Baddiley also took part in work on penicillin synthesis under Professor Todd's direction—see p. 377.)

Dr. M. Weatherall (University of Edinburgh)—personal and expenses: pharmacological studies of "British-Anti-Lewisite" and related chemical substances (under the direction of Professor J. H. Gaddum).

Mr. A. H. M. Wheatley (City Mental Hospital, Cardiff)—personal and expenses: effect of trinitrotoluene and related substances on the metabolism of isolated intact tissues (under the direction of Dr. J. Pryde).

Dr. R. T. Williams (University of Liverpool)—expenses: metabolism of sulphonamide drugs.

Professor A. Wormall (St. Bartholomew's Hospital Medical College, London—working at Cambridge)—assistance by Dr. J. C. Boursnell and Miss H. M. Dewey: action of mustard gas and related substances on proteins and other tissue constituents; vitamin C survey of medical students; studies of the trypanocidal drug suramin.

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PATHOLOGY

The late Professor J. Shaw Dunn (University of Glasgow)—assistance by Dr. E. Duffy, and expenses: experimental alloxan diabetes.

Professor Sir Howard Florey (University of Oxford)—expenses: studies of lysozyme. (See also pp. 351 and 377.)

Dr. Mary Gilmour (Marie Curie Hospital, London)—personal: experimental and clinical studies of malignant tumours.

Professor H. N. Green (University of Sheffield)—expenses: mode of action of the sulphonamide group of drugs; studies of growth-promoting and growth-inhibiting extracts in relation to carcinogenesis. (See also p. 351.)

Dr. Margaret A. Jennings (University of Oxford)—personal (see also p. 377): experimental studies of intestinal function, with special reference to duodenal and gastric secretion (under the direction of Sir Howard Florey).

Dr. (now Professor) E. J. King and the late Dr. T. H. Belt (British Postgraduate Medical School, London)—assistance by Dr. A. A. Ferris and Dr. R. Schade, and expenses: experimental studies of pneumoconiosis. (See also p. 386.)

Dr. J. G. Stephens (University of Oxford)—personal: problems of splenic function, with special reference to the mechanism of red blood cell behaviour (under the direction of Sir Howard Florey).

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BACTERIOLOGY

Dr. J. Gordon (University of Leeds)—expenses: experimental gas gangrene; bactericidal power of serum; studies of *H. influenzae;* bacteriology of burns.

Professor J. W. McLeod (University of Leeds)—expenses: bacteriology of war wounds; experimental gas gangrene; control of penicillin therapy, with special reference to the treatment of bacterial endocarditis (p. 90); rationale of sulphonamide action; studies of *C. diphtheriae*.

Professor Wilson Smith (University of Sheffield)—assistance by Mrs. M. M. Smith, and expenses: sulphonamide and serum therapy in pneumonia; staphylococcus coagulase; penicillin resistance; use and control of penicillin in bacterial endocarditis (p. 90) and in neurosurgery; action of gorse extracts (with Dr. A. Wilson, p. 355, and Professor G. R. Clemo, p. 375).

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The late Professor H. D. Wright (University of Liverpool)—expenses: cross-infection in diphtheria wards.

P. R. ALLISON, J. GORDON and K. ZINNEMANN—
The incidence and significance of *H. influenzae* in chronic bronchiectasis. *J. Path. Bact.*, 1943, **55**, 465.

H. BURTON, J. W. MCLEOD, T. S. MCLEOD and A. MAYR-HARTING—
On the relationships between the respiratory activities of bacteria and their sensitiveness to sulphanilamide, *p*-hydroxylamino- and *p*-nitrobenzenesulphonamide. *Brit. J. exp. Path.*, 1940, **21**, 288.

H. BURTON, J. W. MCLEOD, A. MAYR-HARTING and N. WALKER—
Development of colours from sulphonamides (*p*-nitrobenzenesulphonamide) under bacterial action and the bearing of such phenomena on the theory of the bacteriostatic and bactericidal activities of the sulphonamides. *J. Path. Bact.*, 1942, **54**, 407.

H. BURTON and N. WALKER—
The complex-formation and rearrangement of *p*-hydroxylamino-benzenesulphonamide. *J. Chem. Soc.*, 1943, p. 656.

G. R. CAMERON, M. E. DELAFIELD and J. WILSON—
Pathological changes produced in rats and mice by a toxic fraction derived from *Bact. typhi murium*. *J. Path. Bact.*, 1940, **51**, 223.

K. E. COOPER, F. C. HAPPOLD, K. I. JOHNSTONE, J. W. MCLEOD, H. E. DE C. WOODCOCK and K. S. ZINNEMANN—
Laboratory diagnosis of diphtheria. Comparative values of various media. *Lancet*, 1940, **i**, 865.

J. GORDON—
Inhibition of the anaphylactic reaction by congo red. *J. Path. Bact.*, 1940, **51**, 460.

J. GORDON and W. R. ATKIN—
The effects of sodium hexametaphosphate (calgon) on the complement action of serum. *Brit. J. exp. Path.*, 1941, **22**, 226.

J. GORDON, R. A. HALL, R. M. HEGGIE and E. A. HORNE—
A histological and bacteriological study of healing burns with an inquiry into the significance of local infection. *J. Path. Bact.*, 1946, **58**, 51.

J. GORDON and M. GORDON—
Involution forms of the genus *Vibrio* produced by glycine. *J. Path. Bact.*, 1943, **55**, 63.

J. GORDON and K. I. JOHNSTONE—
The bactericidal action of normal sera. *J. Path. Bact.*, 1940, **50**, 483.
Differentiation between members of the genus *Vibrio* by the bactericidal technique. *Ibid.*, 1942, **54**, 221.

J. GORDON and J. W. MCLEOD—
A simple and rapid method of distinguishing *Cl. novyi* (*B. oedematiens*) from other bacteria associated with gas gangrene. *J. Path. Bact.*, 1940, **50**, 167.
Relative value of sulphonamides and antisera in experimental gas gangrene. *Lancet*, 1941, **i**, 407.

J. GORDON and N. WALKER—
Features in the congo red molecule associated with the inactivation of complement. *J. Path. Bact.*, 1945, **57**, 451.

J. GORDON, H. E. DE C. WOODCOCK and K. ZINNEMANN—
Meningitis due to Pittman and non-Pittman strains of *H. influenzae*. *Brit. med. J.*, 1944, **i**, 779.

J. GORDON and K. ZINNEMANN—
The bactericidal power of guinea-pig serum on *H. influenzae*. *J. Path. Bact.*, 1944, **56**, 55.

M. GORDON and C. HIGGINBOTTOM—
A medium showing a distinctive green colouration with growths of *C. diphtheriae intermedius*. *J. Path. Bact.*, 1942, **54**, 435.

M. GORDON and K. ZINNEMANN—
The *in-vitro* sensitivity of *H. influenzae* to penicillin with special reference to meningeal strains of Pittman's type b. *Brit. med. J.*, 1945, **ii**, 795.

J. H. HALE and W. SMITH—
The influence of coagulase on the phagocytosis of staphylococci. *Brit. J. exp. Path.*, 1945, **26**, 209.

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K. I. JOHNSTONE—
The relationship of the oxidation-reduction potentials developed in bacterial cultures to the production of hydrogen peroxide. *J. Path. Bact.*, 1940, **51**, 59.
The significance of the potentials developed at noble metal electrodes immersed in cultures of *Bact. coli* in a synthetic medium. *Ibid.*, 1942, **54**, 25.
A simple technique for the cultivation of organisms from single cells. *Ibid.*, 1943, **55**, 159.

K. I. JOHNSTONE and K. ZINNEMANN—
An improved unheated blood tellurite medium for the diagnosis of *C. diphtheriae*. *J. Path. Bact.*, 1943, **55**, 53.

J. W. MCLEOD—
The types mitis, intermedius and gravis of *Corynebacterium diphtheriae*. *Bact. Rev.*, 1943, **7**, 1.

J. W. MCLEOD, A. MAYR-HARTING and N. WALKER—
The influence of access of free oxygen on the action of antiseptics with special reference to the sulphonamides. *J. Path. Bact.*, 1944, **56**, 377.
Observations on the bactericidal and bacteriostatic actions of *p*-aminobenzene-sulphonamide and *p*-hydroxylaminobenzene-sulphonamide, with special reference to their suppression by *p*-aminobenzoic acid. *Brit. J. exp. Path.*, 1944, **25**, 27.

D. T. ROBINSON, J. W. MCLEOD and A. W. DOWNIE—
Dust in surgical theatres as a possible source of postoperative tetanus. *Lancet*, 1946, **i**, 152.

W. SMITH and J. H. HALE—
The nature and mode of action of staphylococcus coagulase. *Brit. J. exp. Path.*, 1944, **25**, 101.

W. SMITH and M. M. SMITH—
Bacterial contamination of cerebrospinal fluid. *Lancet*, 1941, **ii**, 783.
Production of sterile and stable penicillinase. *Ibid.*, 1945, **i**, 809.

W. SMITH and A. WILSON—
Effect on the uterus of extracts of gorse (*Ulex gallii*). *Brit. med. J.*, 1943, **ii**, 322.

G. S. WILSON, H. SCHWABACHER and I. MAIER—
The effect of the desensitisation of tuberculous guinea-pigs. *J. Path. Bact.*, 1940, **50**, 89.

H. D. WRIGHT, H. R. SHONE and J. R. TUCKER—
Cross infection in diphtheria wards. *J. Path. Bact.*, 1941, **52**, 111.

K. ZINNEMANN—
Infection of white mice with the three types of *C. diphtheriae*. *J. Path. Bact.*, 1940, **50**, 243.
Toxin production by the three types of *C. diphtheriae*. *Ibid.*, 1943, **55**, 275.

PARASITOLOGY

Professor P. A. Buxton (London School of Hygiene and Tropical Medicine)—assistance by Dr. J. R. Busvine, Dr. W. A. L. David, Mr. W. L. P. Smyly, Mr. P. Bracey and Mrs. S. Barnes, and expenses: control of the louse with fumigants and insecticides (p. 70); studies of anti-mosquito sprays and insect repellents; use of DDT for the control of the bed-bug (p. 72).

Sir Rickard Christophers (University of Cambridge)—expenses: studies of mosquito repellents.

Professor R. T. Leiper (London School of Hygiene and Tropical Medicine)—assistance by Miss M. Young, and expenses: incidence of helminth infections in Britain.

Dr. K. Mellanby (Sorby Research Institute, Sheffield)—expenses: parasitology, transmission and treatment of scabies in human volunteers (p. 72). (See also pp. 65 and 366.)

S. BARNES—
The toxicity of distempers containing DDT. *J. Oil Col. Chem. Ass.*, 1945, **28**, 181.
The residual toxicity of DDT to bed-bugs (*Cimex lectularius* L.) *Bull. ent. Res.*, 1945, **36** 273.
The influence of certain biological factors on the resistance of bed-bugs to DDT (*Cimex lectularius* L.). *Ibid.*, 1945, **36**, 419.

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W. C. BARTLEY and K. MELLANBY—
The parasitology of human scabies (women and children). *Parasitology*, 1944, **35**, 207

J. R. BUSVINE—
Domestic entomology in war-time. *Nature, Lond.*, 1942, **149**, 295.
Home-life of the bed-bug. *Lancet*, 1942, **i**, 453.
The toxicity of some common fumigants to body lice. *Bull. ent. Res.*, 1943, **34**, 19.
Destruction of lice in clothing by hot and cold air. *Ibid.*, 1944, **35**, 115.
Some pioneer work on protection against body lice by the use of lasting insecticides. *Ibid.*, 1945, **36**, 23.

J. R. BUSVINE and P. A. BUXTON—
A new method of controlling the head louse. *Brit. med. J.*, 1942, **i**, 464.

W. A. L. DAVID—
Delousing of clothing by fumigation. *Brit. med. J.*, 1943, **ii**, 108.
Fumigation as a method of controlling the body louse, *Pediculus humanus corporis*, de Geer. Parts I & II. *Bull. ent. Res.*, 1944, **35**, 79. Part III. Practical tests. *Ibid.* 1944, **35**, 101.

W. A. L. DAVID and P. BRACEY—
Activation of pyrethrins in fly-sprays. *Nature, Lond.*, 1944, **153**, 594.

C. G. JOHNSON—
Taxonomic characters, variability, and relative growth in *Cimex lectularius* L. and *C. columbarius* Jenyns (Heteropt. Cimicidae). *Trans. R. Ent. Soc. Lond.*, 1939–40, **89**, 543.
Development, hatching and mortality of the eggs of *Cimex lectularius* L. (Hemiptera) in relation to climate, with observations on the effects of preconditioning to temperature. *Parasitology*, 1940, **32**, 127.
The longevity of the fasting bed-bug (*C. lectularius* L.) under experimental conditions and particularly in relation to the saturation deficiency law of water-loss. *Ibid.*, 1940, **32**, 239.
The maintenance of high atmospheric humidities for entomological work with glycerol-water mixtures. *Ann. appl. Biol.*, 1940, **27**, 295.

C. G. JOHNSON and K. MELLANBY—
The parasitology of human scabies. *Parasitology*, 1942, **34** 285.

K. MELLANBY—
Scabies. Oxford University Press, 1943.
The development of symptoms, parasitic infection and immunity in human scabies. *Parasitology*, 1944, **35**, 197.
Experiments on scabies prophylaxis. *Brit. med. J.*, 1944, **i**, 689.
Control of crab lice. *Ibid.*, 1944, **i**, 720.
Scabies prophylaxis with " tetmosol " soap. *Ibid.*, 1945, **i**, 38.

K. MELLANBY, C. G. JOHNSON and W. C. BARTLEY—
The treatment of scabies. *Brit. med. J.*, 1942, **ii**, 1.

K. MELLANBY, C. G. JOHNSON, W. C. BARTLEY and P. BROWN—
Experiments on the survival and behaviour of the itch mite, *Sarcoptes scabiei* DeG, *var. hominis*. *Bull. ent. Res.*, 1942, **33**, 267.

K. MELLANBY, A. L. NORTHEDGE and C. G. JOHNSON—
Scabies and intelligence. *Lancet*, 1942, **ii**, 596.

M. R. YOUNG—
Threadworms in children in England. *Proc. R. Soc. Med.*, 1942, **35**, 684.

HUMAN GENETICS

The following papers deal with studies assisted by grants before the war:—

O. MAAS and A. S. PATERSON—
Genetic and familial aspects of dystrophia myotonica. *Brain.*, 1943, **66**, 55.

J. R. MUTCH—
Hereditary corneal dystrophy. *Brit. J. Ophthal.*, 1944, **28**, 49.

T. WHITE—
Linkage and crossing-over in the human sex chromosomes. *J. Genet.*, 1940, **40**, 403.

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XV

POSTGRADUATE STUDENTSHIPS AND RESEARCH FELLOWSHIPS

Before the war the Council awarded a series of Studentships and Fellowships in clinical science and experimental pathology, which were intended primarily to provide opportunities for training young medical graduates for research and academic posts in these fields. The scheme had to be suspended owing to wartime difficulties, but Dr. D. A. K. Black and Dr. Jean M. Cass were able to complete the second year of tenure of their Fellowships under Professor L. J. Witts at Oxford and Professor J. C. Spence at Newcastle, respectively. On the expiry of his Fellowship, Dr. Black was awarded a Beit Memorial Fellowship; his subsequent work with Professor McCance at Cambridge has been mentioned on pp. 100, 274-5 and 364-5.

A new series of medical Studentships for training in methods of experimental psychology under the direction of Professor F. C. Bartlett at Cambridge was later instituted, and awards were made to Dr. R. B. Buzzard, Dr. D. R. Davis, Dr. N. Mackworth, Dr. Cecilia Lutwak-Mann, and Dr. Elizabeth Whatley. On completion of their Studentships, the first three named were appointed to the Council's staff in the Applied Psychology Research Unit at Cambridge (p. 319).

A Studentship for training in methods of clinical research under the direction of Professor L. J. Witts at Oxford was also awarded to Dr. P. C. Reynell.

In 1944 the Council decided to replace the former series of Studentships in particular subjects by a more general scheme for the award of Studentships for training in research methods to recent medical and scientific graduates of special promise. During the period under review Studentships of this type were awarded to the following in the fields of chemotherapy and biochemistry:—

Dr. J. A. Barltrop, Mr. R. J. S. Beer, Miss H. Muir, Mr. J. B. Poole, Mr. S. G. Waley and Dr. J. P. Wilson: under Sir Robert Robinson at Oxford University.

Mr. P. C. Crofts: under Professor G. M. Bennett at King's College, London.

Mr. D. Ellis: under Professor J. W. Cook at Glasgow University.

Mr. J. O. Keneford: under Dr. J. C. E. Simpson at the Liverpool School of Tropical Medicine.

Mr. T. J. King: under Dr. F. E. King at Oxford University.

Mr. P. E. Macey: under the late Professor J. M. Gulland at University College, Nottingham.

Mr. J. E. McKail: under Dr. W. O. Kermack at the Royal College of Physicians' Laboratory, Edinburgh.

Mr. J. G. W. Porter: under Dr. F. G. Mann at Oxford University.

Mr. P. Sykes: under Professor A. R. Todd at Cambridge University.

R. G. Bickford—
The fibre dissociation produced by cooling human nerves. *Clin. Sci.*, 1939, **4**, 159.

D. A. K. Black—
Basal metabolism in gastro-intestinal bleeding. *Lancet*, 1940, **i**, 173.
Azotaemia in gastro-duodenal haemorrhage. *Quart. J. Med.*, 1942, n.s. **11**, 77.

D. A. K. Black and A. Leese—
Nitrogen and chloride metabolism in gastro-duodenal haemorrhage. *Quart. J. Med.*, 1940, n.s. **9**, 129.

D. A. K. Black, J. F. Powell and A. F. Smith—
Inulin and perabrodil clearance after alimentary haemorrhage in man. *J. Physiol.*, 1941, **99**, 344.

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J. M. CASS—
Bacillus lactis aerogenes infection in the newborn. *Lancet*, 1941, **i**, 346.

L. I. M. CASTLEDEN—
The effect of potassium salts on cardiac irregularities. *Brit. med. J.*, 1941, **i**, 7.

A. H. CRUICKSHANK—
Anti-lymphocytic serum. *Brit. J. exp. Path.*, 1941, **22**, 126.

J. HARDMAN—
Asymmetry of the skull in relation to subdural collections of fluid. *Brit. J. Radiol.*, 1939, n.s. **12**, 455.
The angioarchitecture of the gliomata. *Brain*, 1940, **63**, 91.

D. JENNINGS—
Perforated peptic ulcer: changes in age-incidence and sex-distribution in the last 150 years. *Lancet*, 1940, **i**, 395 and 444.

Kathleen Schlesinger Research Fellowship

This Fellowship, endowed by the late Mr. Eugen M. Schlesinger and Mrs. Schlesinger in memory of their daughter, is intended for research on cysts of the brain and allied conditions. The Fellowship was held by Dr. Gwenvron M. Griffiths from 1939 until 1941, and has since been temporarily in abeyance.

Fellowships in Tropical Medicine

The scheme of research Fellowships in tropical medicine was in abeyance during the war, and no new appointments were made during the period under review. Dr. J. L. Dales and Dr. S. G. Cowper, who had been appointed to Junior Fellowships in 1937 and 1938, respectively, were called up on active service at the outbreak of war. Of the other Junior Fellows appointed in 1938, Dr. W. H. R. Lumsden continued to work at the Liverpool School of Tropical Medicine until being mobilised in February, 1941, and Dr. A. J. Haddow completed the tenure of his Fellowship, the last year of which was spent in field studies in East Africa. Dr. D. R. Seaton, who was appointed a Junior Fellow in 1939, worked at Liverpool before being called up in 1942.

Dr. C. J. Hackett and Dr. F. Hawking concluded their Senior Fellowships in this country, and Dr. Hawking was subsequently appointed to the Council's staff at the National Institute for Medical Research (p. 203).

R. M. GORDON and D. R. SEATON—
A histological comparison of the effects of certain drugs on scabies, as studied in rodent infections. *Ann. trop. Med. Parasit.*, 1941, **35**, 247.
Observations on the treatment of scabies. *Brit. med. J.*, 1942, **i**, 685.

A. J. HADDOW—
The influence of nutrition on egg-production and longevity in unmated female body-lice (*Pediculus humanus corporis*: Anoplura). *Parasitology*, 1941, **33**, 40.

W. H. R. LUMSDEN and D. S. BERTRAM—
Observations on the biology of *Plasmodium gallinaceum* Brumpt, 1935, in the domestic fowl, with special reference to the production of gametocytes and their development in *Aëdes aegypti* (L). *Ann. trop. Med. Parasit.*, 1940, **34**, 135.
The effect of plasmoquine and of praequine on the subsequent development of the gametocytes of *Plasmodium gallinaceum* Brumpt, 1935, in *Aëdes aegypti* (L). *Ibid.*, 1940, **34**, 161.

D. R. SEATON and W. H. R. LUMSDEN—
Observations on the effects of age, fertilization and light on biting by *Aëdes aegypti* (L) in a controlled microclimate. *Ann. trop. Med. Parasit.*, 1941, **35**, 23.

Travelling Fellowships

No awards of this type were made by the Council during the war, and of the candidates who had been awarded Rockefeller Travelling Fellowships in Medicine for the academic year 1939-40, only Dr. R. M. Kark was able to take up his appointment at the time. He worked on problems of nutrition, pigment metabolism and haemorrhage, under Dr. W. B. Castle and Dr.

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G. R. Minot at Boston. These Fellowships were, however, resumed at the end of the period under review, when the Rockefeller Foundation of New York again generously provided funds for the purpose, and the following awards were made for the academic year 1945-46:—

Dr. G. S. Dawes, Department of Pharmacology, Oxford University.

Dr. J. L. Henderson, Department of Child Life and Health, Edinburgh University (originally elected to a Fellowship in 1939).

Lt.-Col. R. S. Illingworth, late Officer-in-charge of a Medical Division, R.A.M.C. (originally elected to a Fellowship in 1939).

Lt.-Col. W. A. Law, late Officer-in-charge of a Surgical Division, R.A.M.C.

Lt.-Col. N. H. Martin, late Assistant Director of Pathology, 21 Army Group and B.A.O.R.

Dr. R. M. Mayon-White, Physiological Laboratory, Armoured Fighting Vehicle Training School, Lulworth.

Dr. R. L. Richards, Assistant Physician, Neurovascular Unit, E.M.S. Hospital, Gogarburn, Edinburgh.

The Dorothy Temple Cross Research Fellowships in Tuberculosis were resumed a year later, and details of the post-war awards which have been made under this head will be given in the next Report.

R. KARK and A. W. SOUTER—
Synthetic vitamin K in treatment of hypoprothrombinaemia. *Lancet*, 1940, **i**, 1149. The response to vitamin K: a liver-function test. *Ibid.*, 1941, **ii**, 693.

R. KARK, E. L. LOZNER and A. P. MEIKLEJOHN—
Negative effect of synthetic vitamin B_6 hydrochloride in nutritional deficiency in man. *Proc. Soc. Exp. Biol., N.Y.*, 1940, **43**, 97.

R. KARK, A. W. SOUTER and J. C. HAYWARD—
A haemorrhagic diathesis in idiopathic steatorrhoea: observations on its association with vitamin K deficiency. *Quart. J. Med.*, 1940, n.s. **9**, 247.

I. MACKENZIE and J. G. KIDD—
Incidence and specificity of the antibody for a distinctive constituent of the Brown-Pearce tumor. *J. exp. Med.*, 1945, **82**, 41.

I. MACKENZIE and P. ROUS—
The experimental disclosure of latent neoplastic changes in tarred skin. *J. exp. Med.*, 1941, **73**, 391.

N. C. OSWALD—
Behavior of tubercle bacilli following their intravenous injection into a resistant animal (rat). *Arch. Path.*, 1940, **29**, 678.

G. E. SMYTH—
The significance of lesions in the dentate nuclei apparently consecutive to disease of the frontal lobes. *Brain*, 1941, **64**, 63.

A. W. SOUTER and R. KARK—
Quick's prothrombin test simplified by the use of a stable thromboplastin. *Amer. J. med. Sci.*, 1940, **200**, 603.

A. W. SOUTER, R. KARK and F. H. L. TAYLOR—
A stable thromboplastin for use in Quick's prothrombin test. *Science*, 1940, **91**, 532.

J. O. WESTWATER—
Antibody formation in a tuberculous lesion at the site of inoculation. *J. exp. Med.*, 1940, **71**, 455.

F. W. WHITE, A. P. MEIKLEJOHN, E. DEUTSCH and R. KARK—
A comparison of three urobilinogen tests in the urine. (The Watson, Sparkman and Wallace and Diamond methods) in jaundice and diseases of the liver. *Amer. J. digestive Dis.*, 1941, **8**, 346.

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XVI

CONCLUSION

Obituary

The following deaths that have occurred since 1939 are recorded with deep regret. In some instances fuller references have been made at appropriate points in the preceding text.

Members and Former Members of Council

Professor A. J. Clark, F.R.S., of the Chair of Materia Medica in the University of Edinburgh, died during his period of office as a Member of the Council (1941). The following deaths occurred among former Members:—Dr. W. W. C. Topley, F.R.S., formerly Professor of Bacteriology and Immunology at the London School of Hygiene and Tropical Medicine and latterly Secretary of the Agricultural Research Council (1944, see pp. 28 and 161); Sir Cuthbert S. Wallace, Bart., K.C.M.G., F.R.C.S., Consulting Surgeon, St. Thomas's Hospital, London (1944, see p. 28); Sir John C. G. Ledingham, C.M.G., F.R.S., formerly Director of the Lister Institute of Preventive Medicine (1944); Dr. J. A. Arkwright, F.R.S., formerly of the Lister Institute of Preventive Medicine (1944); the Rt. Hon. Viscount Dawson of Penn, G.C.V.O., F.R.C.P., Consulting Physician to the London Hospital (1945, see p. 69); and Sir Thomas Lewis, C.B.E., F.R.S., Director of the Department of Clinical Research, University College Hospital Medical School, London (1945, see pp. 26 and 249).

Members of the Council's Staff

The Council also suffered the loss, through death, of the following established and temporary members of their scientific staff while still in active work:—Dr. R. J. Lythgoe, University College, London (1940); Sir Patrick P. Laidlaw, F.R.S., Deputy Director of the National Institute for Medical Research (1940, see pp. 25 and 213); Dr. Matthew Young, University College, London (1940); Mr. H. P. Marks, National Institute for Medical Research (1944, see p. 205); Dr. G. L. Taylor, Galton Laboratory Serum Unit, Cambridge (1945, see p. 190); Dr. A. Sand, F.R.S., attached to the National Institute for Medical Research (1945, see p. 207); and Dr. K. J. W. Craik, Director of the Applied Psychology Research Unit, Cambridge (1945, see pp. 133, 134 and 319). Dr. F. Griffith and Dr. W. M. Scott, temporarily seconded to the Council's service from the Ministry of Health, were killed in London by enemy action on the 16th April, 1941 (see p. 165).

Retirements from the Council's Staff

The Council have lost the services of the following members of their staff through retirement on reaching the age limit:—Sir Henry H. Dale (p. 26); Sir Percival Hartley; Dr. A. Stanley Griffith (since deceased); Dr. J. Argyll Campbell (since deceased); Dr. Julia Bell; Dr. May Smith; Dr. R. St. John-Brooks; Dr. E. J. H. Schuster; and Miss K. Baverstock.

The following among the more senior members of the established staff have left the Council's service to take up other work:—Air Vice-Marshal Sir David Munro, to be Chief Medical Officer to the Ministry of Supply (since retired); Dr. F. G. Young to be Professor of Biochemistry at St. Thomas's Hospital Medical School, London (now Professor of Biochemistry at University College,

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London); Dr. A. N. Drury, to be Director of the Lister Institute of Preventive Medicine; Dr. C. Rimington, to be Professor of Chemical Pathology at University College Hospital Medical School, London; Dr. M. van den Ende, to be Professor of Bacteriology in the University of Cape Town; and Dr. Dorothy S. Russell, to be Professor of Morbid Anatomy at the London Hospital Medical College.

Honours

Since 1939 the following Honours have been conferred by His Majesty on members or retired members of the Council's staff:—

O.M., G.B.E.	Sir Henry H. Dale.
Knighthood	Dr. Percival Hartley; Dr. Paul G. Fildes.
C.M.G.	Dr. B. S. Platt.
C.B.E.	Dr. E. A. Carmichael: Dr. A. N. Drury; Dr. R. B. Bourdillon; Dr. G. L. Brown.
O.B.E.	Dr. Janet Vaughan; Dr. May Smith; Dr. E. J. H. Schuster.

In addition, Professor G. S. Wilson was appointed Honorary Physician to the King for the period 1944-47.

The Council also noted with gratification the following other awards for services in the general field of medical research:—

O.M.	Professor E. D. Adrian.
Knighthood.	Professor A. Fleming; Professor H. W. Florey; Professor E. L. Kennaway.

The following workers in the Council's service have been admitted to the Fellowship of the Royal Society since 1939:—

Dr. A. Felix, Dr. L. Colebrook, Dr. Marjory Stephenson, Dr. G. L. Brown and Professor H. A. Krebs.

Advisers and Committees

Apart from all the help which they constantly receive from members of their own scientific staff, the Council have throughout the period covered by this Report been indebted to very many independent experts for technical advice in special subjects. Collaboration in work actually described in the foregoing pages has been acknowledged as far as possible, but this still leaves many cases of which it is impracticable to make separate mention. The Council are especially indebted to those who have served on their various committees, and lists of the members of such of these bodies as were active during the period under review are given in Appendix E. For all assistance of this kind, the Council wish here to express their warm gratitude.

Headquarters Office

From the beginning of the war until the end of 1945 the Headquarters Office of the Council was temporarily accommodated in the London School of Hygiene and Tropical Medicine, to the authorities and staff of which the sincere thanks of the Council and their officers are due for this facility and for the agreeable personal contacts which it entailed.

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The writing of this Report, covering so long a period of such varied activity, has inevitably been a heavy and protracted task, to which many hands have contributed. The main burden of the detailed editorial work has fallen on Dr. F. H. K. Green, Publications Officer till 1946 and now Assistant Secretary, latterly helped by Dr. Martin Ware, his successor in the former post, and with assistance by Miss E. Wigmore, Librarian at the National Institute for Medical Research, in respect of the many references to publications.

BALFOUR OF BURLEIGH,

Chairman of the
Medical Research Council.

EDWARD MELLANBY,
Secretary of the Council,
38, Old Queen Street,
Westminster,
London, S.W.1.

September, 1947.

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APPENDIX A

PUBLICATIONS OF THE MEDICAL RESEARCH COUNCIL SINCE SEPTEMBER 1939

(Prices in brackets include postage.)

Special Report Series

No. 238. The Structure of Teeth as shown by X-ray Examination. By J. Thewlis. [1940.] 2*s.* 6*d.*; (2*s.* 9*d.*).

No. 239. A Comparative Study of the Seasonal Incidence of Mortality in England and Wales and in the United States of America. By E. Lewis-Faning. [1940.] 1*s.*; (1*s.* 2*d.*).

No. 240. Pathogenic Anaerobic Organisms of the Actinomyces Group. By Dagny Erikson. [1940.] *(Out of print).*

No. 241. Dental Disease in the Island of Lewis. By J. D. King. [1940.] 1*s.*; (1*s.* 2*d.*).

No. 242. Studies in Nutrition: an Inquiry into the Diet of Families in the Highlands and Islands of Scotland. By E. P. Cathcart, A. M. T. Murray and J. B. Beveridge. [1940.] *(Out of print).*

No. 243. Chronic Pulmonary Disease in South Wales Coalminers: I.—Medical Studies. A.—Report by the Committee on Industrial Pulmonary Disease; B.—Medical Survey, by P. D'Arcy Hart and E. A. Aslett, with contributions by D. Hicks and R. Yates; C.—Pathological Report, by T. H. Belt with assistance from A. A. Ferris. [1942.] 10*s.* 6*d.*; (11*s.* 1*d.*).

No. 244. Chronic Pulmonary Disease in South Wales Coalminers: II.—Environmental Studies. A.—Report by the Committee on Industrial Pulmonary Disease; B.–G.—Reports on Physical, Chemical and Petrological Studies, by T. Bedford and C. G. Warner; H. V. A. Briscoe, P. F. Holt, N. Spoor and others; G. Nagelschmidt; A. Brammall and J. G. C. Leech; D. Hicks and G. Nagelschmidt; J. Ivon Graham and D. F. Runnicles; and co-workers. [1943.] 10*s.* 6*d.*; (10*s.* 11*d.*).

No. 245. Report of the Committee on Bed-Bug Infestation, 1935–1940. [1942.] 1*s.*; (1*s.* 2*d.*).

No. 246. Report of the Committee on Tuberculosis in War-time. [1942: reprinted 1943.] 9*d.*; (10*d.*).

No. 247. The Epidemiology of Diphtheria during the last Forty Years. By W. T. Russell. [1943.] 1*s.*; (1*s.* 2*d.*).

No. 248. A Provisional Classification of Diseases and Injuries for Use in Compiling Morbidity Statistics. By the Committee on Hospital Morbidity Statistics. [1944.] 4*s.* 6*d*; (4*s.* 10*d.*).

No. 249. Studies of Burns and Scalds (Reports of the Burns Unit, Royal Infirmary, Glasgow, 1942–43). [1944.] 4*s.*; (4*s.* 5*d.*).

No. 250. Chronic Pulmonary Disease in South Wales Coalminers: III.—Experimental Studies. A.—Report by the Committee on Industrial Pulmonary Disease; B.—The Mineral Content of the Lungs of Workers from the S. Wales Coalfield, by E. J. King and G. Nagelschmidt; C.—The Estimation of Coal and of Aluminium in Dried Lung, by E. J. King and Margaret Gilchrist; D.—Tissue Reactions Produced Experimentally by Selected Dusts from S. Wales Coalmines, by T. H. Belt and E. J. King; E.—The Solubility of Dusts from S. Wales Coalmines, by E. J. King. [1945.] 5*s.*; (5*s.* 4*d.*).

No. 251. Mass Miniature Radiography of Civilians for the Detection of Pulmonary Tuberculosis (Guide to Administration and Technique with a Mobile Apparatus using 35-mm. Film: and Results of a Survey). By Kathleen C. Clark, P. D'Arcy Hart, Peter Kerley and Brian C. Thompson. [1945.] 3*s.*; (3*s.* 3*d.*).

No. 252. Haemoglobin Levels in Great Britain in 1943 (with Observations upon Serum Protein Levels). By the Committee on Haemoglobin Surveys. [1945.] 2*s.*; (2*s.* 3*d.*).

No. 253. Tables of Representative Values of Foods commonly used in Tropical Countries. By B. S. Platt. [1945.] 9*d.*; (11*d.*).

No. 254. An Experimental Study of Rationing. By R. A. McCance and E. M. Widdowson. [1946.] 1*s.*; (1*s.* 2*d.*).

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No. 255. Chemotherapeutic and Other Studies of Typhus. By M. van den Ende, C. H. Stuart-Harris, F. Fulton and J. S. F. Niven, with others. [1946.] 12*s.* 6*d.*; (12*s.* 11*d.*).

No. 256. The Cultivation of Viruses and Rickettsiae in the Chick Embryo. By W. I. B. Beveridge and F. M. Burnet. [1946.] 2*s.*; (2*s.* 2*d.*).

No. 257. A Study of Individual Children's Diets. By E. M. Widdowson. [1947.] 6*s.*; (6*s.* 5*d.*).

No. 258. The Preservation of Proteins by Drying, with special reference to the Production of Dried Human Serum and Plasma for Transfusion. By R. I. N. Greaves. [1946.] 2*s.*; (2*s.* 2*d.*).

No. 259. The Murine Type of Tubercle Bacillus (The Vole Acid-fast Bacillus). By A. Q. Wells and A. H. T. Robb-Smith. [1946.] 2*s.*; (2*s.* 2*d.*).

No. 260. The Bacteriology of Spray-Dried Egg, with particular reference to Food Poisoning. By various authors. [1947.] 1*s.*; (1*s.* 2*d.*).

No. 261. Hearing Aids and Audiometers. Report of the Committee on Electro-Acoustics. [1947.] 1*s.* 3*d.*; (1*s.* 5*d.*).

War Memoranda

No. 1. The Treatment of "Wound Shock". (Instructions produced by the Medical Research Council Committees on Traumatic Shock and on Blood Transfusion, in co-operation with the Army Medical Service.) First published 1940. Revised edition, 1944. 6*d.*; (7*d.*).

No. 2. Notes on Gas Gangrene—Prevention: Diagnosis: Treatment (with an account of the technique of wound-excision, and a scheme for the bacteriological investigation of war wounds). First published 1940. Revised edition, 1943. 6*d.*; (7*d.*).

No. 3. Economy in the Use of Drugs in War-time. First published 1941. Revised edition, 1944. 3*d.*; (4*d.*).

No. 4. A Glossary of Psychological Terms commonly used in Cases of Head Injury. [1941.] 1*d.*; (2*d.*).

No. 5. Emergency Amputations. [1941.] 2*d.*; (3*d.*).

No. 6. The Prevention of "Hospital Infection" of Wounds. First published 1941. Reprinted, with minor amendments, 1942 and 1943. 6*d.*; (7*d.*).

No. 7. Aids to the Investigation of Peripheral Nerve Injuries. First published, 1942. Revised edition, 1943. 2*s.*; (2*s.* 2*d.*).

No. 8. A Guide to the Preservation of Life at Sea after Shipwreck. [1943.] 4*d.*; (5*d.*).

No. 9. The Determination of Blood Groups. [1943.] Reprinted 1944. 4*d.*; (5*d.*).

No. 10. The Medical Use of Sulphonamides. By various authors. Edited by F. Hawking and F. H. K. Green. First published 1943. Revised edition, 1945. 1*s.* 3*d.*; (1*s.* 5*d.*).

No. 11. The Control of Cross Infection in Hospitals. First published 1944. Reprinted with minor amendments and additions, September, 1944. 6*d.*; (7*d.*).

No. 12. The Use of Penicillin in Treating War Wounds. Instructions prepared by the Penicillin Clinical Trials Committee. [1944.] 3*d.*; (4*d.*).

No. 13. Arterial Injuries: Early Diagnosis and Treatment. [1944]. 4*d.*; (5*d.*).

No. 14. Nutritive Values of Wartime Foods. Tables compiled for the Accessory Food Factors Committee. [1945.] 1*s.*; (1*s.* 2*d.*).

No. 15. The Sterilization, Use and Care of Syringes. [1945.] 4*d.*; (5*d.*).

No. 16. Food Yeast: a Survey of its Nutritive Value. [1945]. 3*d.*; (4*d.*).

No. 17. Environmental Warmth and its Measurement. A book of reference prepared for the Royal Naval Personnel Research Committee of the Medical Research Council by T. Bedford. [1946.] 9*d.*; (11*d.*). *Supplement*, 1*s.* 6*d.*; (1*s.* 9*d.*).

Bulletin of War Medicine

The *Bulletin of War Medicine*, which was produced with the co-operation of the staff of the Bureau of Hygiene and Tropical Diseases (p. 201), contains abstracts of articles in all branches of medicine, surgery and kindred subjects with a bearing on war problems, culled from the British and foreign medical and scientific press. Vols. I and II were published two-monthly at 2*s.* 6*d.* a copy; Vols. III–VI, published monthly at 1*s.* 3*d.* a copy. Title page and Index to each volume, price 6*d.* Publication of the *Bulletin* ceased with Vol. VI, No. 12 (August, 1946).

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Industrial Health Research Board Reports

Reports in the Board's main Series

No. 84. A Study of Accident Proneness amongst Motor Drivers, by E. Farmer and E. G. Chambers. [1940.] (*Out of print*).
No. 85. The Recording of Sickness Absence in Industry (A Preliminary Report), by a Sub-Committee of the Industrial Health Research Board. [1944.] 4*d*.; (5*d*.).
No. 86. A Study of Certified Sickness Absence among Women in Industry, by S. Wyatt, assisted by R. Marriott, W. M. Dawson, Norah M. Davis, D. E. R. Hughes and F. G. L. Stock. [1945.] 9*d*.; (10*d*.).
No. 87. The Relation between Illumination and Visual Efficiency—the Effect of Brightness Contrast, by H. C. Weston. [1945.] 9*d*.; (10*d*.).
No. 88. A Study of Women on War Work in Four Factories, by S. Wyatt, assisted by R. Marriott, W. M. Dawson, Norah M. Davis, D. E. R. Hughes and F. G. L. Stock. [1945.] 9*d*.; (10*d*.).
No. 89. Artificial Sunlight Treatment in Industry. A Report on the Results of Three Trials—in an Office, a Factory and a Coalmine, by Dora Colebrook. [1946.] 1*s*.; (1*s*. 1*d*.).
No. 90. The Incidence of Neurosis among Factory Workers, by Russell Fraser and others. [1947.] 1*s*. 3*d*.; (1*s*. 4*d*.).

Emergency Reports

No. 1. Industrial Health in War: a Summary of Research Findings capable of Immediate Application in furtherance of the National Effort. [1940.] (Reprinted, 1945.) 6*d*.; (7*d*.).
No. 2. Hours of Work, Lost Time and Labour Wastage. [1942.] 6*d*.; (7*d*.).
No. 3. The Personal Factor in Accidents. [1942.] (Reprinted, 1945.) 4*d*.; (5*d*.).
No. 4. A Study of Absenteeism among Women, by S. Wyatt, R. Marriott and D. E. R. Hughes. [1943.] 2*d*.; (2½*d*.).
No. 5. A Study of Variations in Output by S. Wyatt, assisted by R. Marriott, W. M. Dawson, D. E. R. Hughes and F. G. L. Stock. [1944.] 4*d*.; (5*d*.).

Pamphlets

No. 1. Ventilation and Heating: Lighting and Seeing. [1943.] (Reprinted, 1944.) 3*d*.; (4*d*.).
No. 2. Absence from Work: Prevention of Fatigue. [1944.] 3*d*.; (4*d*.).
No. 3. Why is She Away? The Problem of Sickness among Women in Industry. [1945.] 4*d*.; (5*d*.).
Health Research in Industry. (Proceedings of a Conference on Industrial Health Research held at the London School of Hygiene and Tropical Medicine, 28th September, 1944.) [1945.] 6*d*.; (7*d*.).

Complete lists of the publications of the Medical Research Council and of the Council's Industrial Health Research Board are obtainable, free on request, from H.M. Stationery Office.

APPENDIX B

LIST OF REPORTS AND MEMORANDA SPONSORED BY COMMITTEES OF THE MEDICAL RESEARCH COUNCIL WHICH WERE PUBLISHED IN JOURNALS

Sub-Committee on the Healing of War Fractures

I.—The causes and prevention of delayed union of fractures. *Bull. War Med.*, 1944, **4**, 559.
II.—The avoidance of infection around transfixation pins. *Ibid.*, 1944, **4**, 561.

Nerve Injuries Committee

Note on the assessment of recovery in peripheral nerve injuries. *Bull. War Med.* 1943, **3**, 258.
First-aid and early treatment in traumatic paraplegia. *Ibid.*, 1944, **4**, 431.

Malaria Committee

Mepacrine for malaria: statement by M.R.C. Committee on Malaria. *Lancet*, 1944, **ii**, 667 and *Brit. med. J.*, 1944, **ii**, 664.

Therapeutic Requirements Committee

Economy in the use of bactericides. *Bull. War Med.*, 1942, **2**, 441.

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Penicillin Clinical Trials Committee

An investigation of the therapeutic properties of penicillin : a report to the Medical Research Council. (Barron, J. N., Christie, R. V., Fraser, D. B., Garrod, L. P., Mansfield, O. T., Morgan, H. V., Mowlem, R., Robertson, I. M., Roxburgh, A. C. and Roxburgh, I. A.). *Brit. med. J.*, 1944, **i**, 513.

Penicillin in subacute bacterial endocarditis : report to the Medical Research Council on 147 patients treated in 14 centres appointed by the Penicillin Clinical Trials Committee. (Christie, R. V.). *Lancet*, 1946, **i**, 369 and *Brit. med. J.*, 1946, **i**, 381.

Publications on clinical trials of penicillin by workers who received grants from the Council are listed on pp. 361 and 378 ; numerous other publications by those who received supplies of penicillin through the Penicillin Clinical Trials Committee are omitted from these lists.

Accessory Food Factors Committee

M.R.C. memorandum on bread. *Lancet*, 1940, **ii**, 143.

National flour. *Lancet*, 1941, **i**, 703.

Preparing green vegetables for the table. *Lancet*, 1941, **i**, 838, and *Brit. med. J.* 1941, **ii**, 26.

Vitamin A Sub-Committee

Estimation of vitamin A. (Hume, E. M.). *Nature, Lond.*, 1943, **151**, 535.

Vitamin A deficiency and the requirements of human adults. *Ibid.*, 1945, **156**, 11.

Vitamin B Sub-Committee

The vitamin B_1 content of National Flour and Bread—the results of comparative tests by various methods. *Biochem. J.*, 1943, **37**, 433.

Vitamin E Sub-Committee

Standardisation of vitamin E. (Hume, E. M.). *Nature, Lond.*, 1941, **148**, 472.

Goitre Sub-Committee

Endemic goitre in England : argument for preventive action. *Lancet*, 1944, **i**, 107.

Blood Transfusion Research Committee

The danger of haemolytic transfusion reactions due to immunisation of the recipient to the Rh factor. *Bull. War Med.*, 1943, **3**, 665.

Patulin Clinical Trials Committee

Clinical trial of Patulin in the common cold. *Lancet*, 1944, **ii**, 373.

Military Personnel Research Committee

The following papers published since the end of the war relate to investigations made on behalf of this Committee and its Sub-Committees on Analeptic Substances and on Armoured Fighting Vehicles, respectively :—

D. P. Cuthbertson and J. A. C. Knox—

The effects of analeptics on the fatigued subject. *J. Physiol.*, 1947, **106**, 42.

P. Hugh-Jones—

The effect of limb position in seated subjects on their ability to utilize the maximum contractile force of the limb muscles. *J. Physiol.*, 1947, **105**, 332.

The effect of seat position on the efficiency of bicycle pedalling. *Ibid.*, 1947, **106**, 186.

APPENDIX C

PUBLICATIONS BY MEMBERS OF THE STAFFS OF THE LONDON BLOOD SUPPLY DEPOTS, AND OF THE GALTON BLOOD GROUPING UNIT, CAMBRIDGE

E. F. Aubert, K. E. Boorman and B. E. Dodd—

The agglutinin-inhibiting substance in human serum. *J. Path. Bact.*, 1942, **54**, 89.

E. F. Aubert, K. E. Boorman, B. E. Dodd and J. F. Loutit—

The universal donor with high titre iso-agglutinins. The effect of anti-A iso-agglutinins on recipients of group A. *Brit. med. J.*, 1942, **i**, 659.

K. E. Boorman and B. E. Dodd—

The group-specific substances A, B, M, N and Rh : their occurrence in tissues and body fluids. *J. Path. Bact.*, 1943, **55**, 329.

K. E. Boorman, B. E. Dodd and P. L. Mollison—

The clinical significance of the Rh factor. *Brit. med. J.*, 1942, **ii**, 535 and 569.

The incidence of Haemolytic Disease of the Foetus (" Erythroblastosis Foetalis ") in different families. The value of serological tests in diagnosis and prognosis. *J. Obstet. Gynaec.*, 1944, **51**, 1.

Iso-immunisation to the blood group factors A, B, and Rh. *J. Path. Bact.*, 1945, **57**, 157.

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W. H. Bradley, J. F. Loutit and K. Maunsell—
An episode of "Homologous Serum Jaundice." *Brit. med. J.*, 1944, **ii**, 268.

H. F. Brewer—
Chemotherapy, serotherapy and haemotherapy in otology and laryngology. Opening paper at R.S.M. combined sections of laryngology and otology, May 2nd, 1941. *Proc. R. Soc. Med.*, 1941, **34**, 668.
A note on the Rh factor and its significance. *St. Bart's Hosp. J.*, 1943, War ed. **4**, 48.
Blood transfusion for Red Cross Nurses. London (Cassell & Co. Ltd.), 1945.

H. F. Brewer, G. W. Hayward, K. O. Black, E. C. O. Jewesbury—
Stored blood. An interim survey from the emergency blood supply depot. *St. Bart's Hosp. J.*, 1940, War ed. **1**, 113.

H. F. Brewer, M. Maizels, J. O. Oliver and J. Vaughan—
Transfusion of fresh and stored blood. *Brit. med. J.*, 1940, **ii**, 48.

H. Brown, C. H. Gray and P. L. Mollison—
Treatment of the nephrotic syndrome with serum transfusions. *Brit. med. J.*, 1942, **i**, 515.

G. L. Brown, J. A. R. Miles, J. M. Vaughan and L. E. H. Whitby—
The effect of haemorrhage upon red cell size and red cell distribution. *Brit. med. J.*, 1942, i, 99.

H. A. Brown and P. L. Mollison—
A note on the transfusion of reconstituted dried human serum. *Brit. med. J.*, 1940, **ii**, 821.

S. Callender, R. R. Race and Z. V. Paykoc—
Hypersensitivity to transfused blood. *Brit. med. J.*, 1945, **ii**, 83.

R. R. A. Coombs, A. E. Mourant and R. R. Race—
A new test for the detection of weak and "incomplete" Rh agglutinins. *Brit. J. exp. Path.*, 1945, **26**, 255.
Detection of weak and "incomplete" Rh agglutinins: a new test. *Lancet*, 1945, **ii**, 15.

R. R. A. Coombs and R. R. Race—
Further observations on the "incomplete" or "blocking" Rh antibody. *Nature, Lond.*, 1945, **156**, 233.

J. V. Dacie and P. L. Mollison—
Survival of normal erythrocytes after transfusion to patients with familial haemolytic anaemia (Acholuric jaundice). *Lancet*, 1943, **i**, 550.

C. B. B. Downman, J. O. Oliver and I. M. Young—
Partition of potassium in stored blood. *Brit. med. J.*, 1940, **i**, 559.

J. Dubash, O. Clegg and J. Vaughan—
Changes occurring in blood stored in different preservatives. *Brit. med. J.*, 1940, **ii**, 482.

M. Dyson and G. Plaut—
A study of the accuracy of serum protein estimations and of diurnal variations in their level. *Brit. med. J.*, 1943, **ii**, 6.

M. Dyson, G. Plaut and J. Vaughan—
Changes in the circulating blood in man following blood loss or transfusion of concentrated red cells. *Quart. J. exp. Physiol.*, 1943–44, **32**, 255.

R. A. Fisher, R. R. Race and G. L. Taylor—
Mutation and the Rhesus reaction. *Nature, Lond.*, 1944, **153**, 106.

J. L. Hamilton Paterson, R. R. Race and G. L. Taylor—
A case of human iso-agglutinin anti-M. *Brit. med. J.*, 1942, **ii**, 37.

R. Hudson—
Haemolysis in stored blood plasma. A simple method for its estimation. *Lancet*, 1940, **ii**, 10.

D. Hunter, R. Milton, K. M. A. Perry, H. J. Barrie, J. F. Loutit and T. S. Marshall—
Investigation for signs of benzene intoxication in workers using aeroplane dope and rubber solvents. *Brit. J. industr. Med.*, 1944, **1**, 238.

E. W. Ikin, A. M. Prior, R. R. Race and G. L. Taylor—
The distributions in the A_1A_2BO blood groups in England. *Ann. Eugen., Camb.*, 1939, **9**, 409.

E. C. O. Jewesbury—
The development of blood transfusion. I, II and III. *St. Bart's Hosp. J.*, 1940–41 War ed. **2**, 22, 44 and 65.
Reactions after transfusion of stored blood. *Brit. med. J.*, 1941, **i**, 663.

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A. KYRKE-SMITH—
The storage of blood grouping sera. *Bull. Inst. med. Lab. Technology*, 1945, **11**, 21.

B. J. LAWRENCE and G. PLAUT—
The effect of bleeding on the blood-sugar level in blood donors. *Brit. med. J.*, 1942, **ii**, 8.

J. F. LOUTIT—
Human blood groups. *Nature, Lond.*, 1944, **153**, 97.
Factors influencing the preservation of stored red cells. *J. Path. Bact.*, 1945, **57**, 325.

J. F. LOUTIT and P. L. MOLLISON—
Advantages of a disodium-citrate-glucose mixture as a blood preservative. *Brit. med. J.*, 1943, **ii**, 744.

J. F. LOUTIT, M. D. MOLLISON and E. D. VAN DER WALT—
Venous pressure during venesection and blood transfusion. *Brit. med. J.*, 1942, **ii**, 658.

J. F. LOUTIT, P. L. MOLLISON and I. M. YOUNG—
Citric acid-sodium citrate-glucose mixtures for blood storage. *Quart. J. exp. Physiol.*, 1943–44, **32**, 183.

A. J. MCCALL, R. R. RACE and G. L. TAYLOR—
Rhesus antibody in Rh-positive mother causing haemolytic disease of newborn. *Lancet*, 1944, **i**, 214.

D. H. G. MACQUAIDE and P. L. MOLLISON—
Treatment of anaemia by transfusion of concentrated suspensions of red cells. *Brit. med. J.*, 1940, **ii**, 555.

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Blood volume in chronic anaemia by a concentrated corpuscle-haemoglobin method. *Lancet*, 1943, **i**, 637.

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Preservation of organic phosphorus compounds in stored blood by glucose. *Lancet*, 1941, **i**, 722.
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Processing of plasma with kaolin. *Lancet*, 1944, **ii**, 205.
Intercellular plasma in the centrifuged erythrocytes of normal human blood. *Quart. J. exp. Physiol.*, 1944–45, **33**, 129.

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Preservation of stored blood. *Lancet*, 1939, **ii**, 1219.
Effects of storage on human erythrocytes. *Ibid*, 1940, **i**, 113.

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Urticarial reactions and desensitization in allergic recipients after serum transfusions. *Brit. med. J.*, 1944, **ii**, 236.

P. L. MOLLISON—
The aetiology of erythroblastosis foetalis and certain haemolytic transfusion reactions, with special reference to the Rh factor. *Proc. R. Soc. Med.*, 1943, **36**, 221.
The survival of transfused erythrocytes in haemolytic disease of the newborn. *Arch. Dis. Childh.*, 1943, **18**, 161.
The investigation of haemolytic transfusion reactions. *Brit. med. J.*, 1943, **i**, 529 and 559.
The application of present knowledge about the Rh factor. *Post-Grad. med. J.*, 1944, **20**, 17.

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On the survival of the transfused erythrocytes of stored blood. *Quart. J. exp. Physiol.*, 1940, **30**, 313.
Failure of *in vitro* tests as a guide to the value of stored blood. *Brit. med. J.*, 1941, **ii**, 797.
Isoagglutinin changes after transfusion of incompatible blood and serum. *Lancet*, 1941, **ii**, 635.
In vivo survival in the human subject of transfused erythrocytes after storage in various preservative solutions. *Quart. J. exp. Physiol.*, 1941–42, **31**, 359.

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A new Rhesus antibody. *Nature, Lond.*, 1945, **155**, 542.

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Gastroduodenal haemorrhage treated medically with enthusiastic blood transfusion. *Lancet*, 1943, **ii**, 469.

G. PLAUT, M. L. BARROW and J. M. ABBOTT—
The results of routine investigation for Rh factor at the N.W. London Depot. *Brit. med. J.*, 1945, **ii**, 273.

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On the inheritance and linkage relations of acholuric jaundice. *Ann. Eugen., Camb.*, 1942, **11**, 365.
Some recent observations on the inheritance of blood groups. *Brit. med. Bull.*, 1944, **2**, 165.
An " incomplete " antibody in human serum. *Nature, Lond.*, 1944, **153**, 771.

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Anti-Hr serum of Levine. *Nature, Lond.*, 1945, **155**, 542.

R. R. RACE and G. L. TAYLOR—
A serum that discloses the genotype of some Rh positive people. *Nature, Lond.*, 1943, **152**, 300.
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The rare gene Rh_y in mother and son. *Nature, Lond.*, 1944, **153**, 560.

R. R. RACE, G. L. TAYLOR, K. E. BOORMAN and B. E. DODD—
Recognition of Rh genotypes in man. *Nature, Lond.*, 1943, **152**, 563.

R. R. RACE, G. L. TAYLOR, D. F. CAPPELL and M. N. MCFARLANE—
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Recognition of a further common Rh genotype in man. *Nature, Lond.*, 1944, **153**, 52.

R. R. RACE, G. L. TAYLOR, E. W. IKIN and A. M. DOBSON—
The inheritance of allelomorphs of the Rh gene : a second series of families. *Ann. Eugen., Camb.*, 1945, **12**, 261.

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The Rh blood group factor. *Med. Pr.*, 1944, **211**, 86 and 104.

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An unusually weakly reacting " A " blood-group antigen. *J. Path. Bact.*, 1942, **54**, 261.
A reliable technique for the diagnosis of the ABO blood groups. *Ibid.*, 1942, **54**, 81.
Frequency of the iso-agglutinin $alpha_1$ in the serum of the sub-groups A_2 and A_2B. *Ibid.*, 1942, **54**, 415.
Optimal proportions of antigen and antibody in tests for Rh antibodies. *Brit. med. J.*, 942, **ii**, 572.

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APPENDIX D

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R. F. BRIDGES and JOAN TAYLOR—
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A mild epidemic of undulant fever in a boys' school due to drinking raw milk. *Brit. med. J.*, 1940, **i**, 477.

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APPENDIX E

LIST OF MEMBERS OF THE COUNCIL'S PRINCIPAL COMMITTEES AND SUB-COMMITTEES WHICH WERE ACTIVE DURING THE WAR

War Wounds

The late Sir Cuthbert Wallace, Bart., K.C.M.G., C.B., F.R.C.S. (*Chairman until his death in June*, 1944).
Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P. (*Chairman from June*, 1944).
E. A. Carmichael, C.B.E., M.B., F.R.C.P.
L. Colebrook, M.B., F.R.C.O.G., F.R.S.
Brigadier F. A. E. Crew, M.D., D.Sc., F.R.S., *late* R.A.M.C. (*from June* , 1942).
A. N. Drury, C.B.E., M.D., F.R.S.
The late A. Tudor Edwards, M.D., F.R.C.S.
Sir Thomas Fairbank, D.S.O., O.B.E., M.S., F.R.C.S. (*from March* 1942).
Brigadier D. Fettes, O.B.E., M.B., F.R.C.S., *late* R.A.M.C. (*from February*, 1945).
Professor Sir Howard Florey, M.B., Ph.D., F.R.S.
Sir Claude Frankau, C.B.E., D.S.O., M.S., F.R.C.S.
Professor Sir Francis Fraser, M.D., F.R.C.P.
Professor G. E. Gask, C.M.G., D.S.O., F.R.C.S.
G. R. Gridlestone, D.M., F.R.C.S. (*from January*, 1942).
Surgeon Rear-Admiral Sir Gordon Gordon-Taylor, K.B.E., C.B., M.S., F.R.C.S.
Major-General Sir Charles Gordon-Watson, K.B.E., C.M.G., F.R.C.S., *late* R.A.M.C.
Air Vice-Marshal G. L. Keynes, M.D., F.R.C.S., R.A.F.V.R.
Professor J. R. Learmonth, C.B.E., Ch.M., F.R.C.S.E.
The late Sir John C. G. Ledingham, C.M.G., D.Sc., F.R.C.P., F.R.S.
Professor J. McIntosh, M.D., LL.D.
Major-General D. C. Monro, C.B., C.B.E., M.B., F.R.C.S.E., *late* R.A.M.C. (*from November*, 1942 *to November*, 1944).
Major-General Sir Max Page, K.B.E., C.B., D.S.O., M.S., F.R.C.S., *late* R.A.M.C.
G. Perkins, M.C., M.Ch., F.R.C.S. (*from January*, 1942).
Major-General H. Marrian Perry, C.B., O.B.E., F.R.C.P., *late* R.A.M.C. (*until September*, 1942).
Professor R. S. Pilcher, M.S., M.R.C.P., F.R.C.S.
Major-General L. T. Poole, D.S.O., M.C., K.H.P., *late* R.A.M.C. (*from September*, 1942).
Professor J. Paterson Ross, M.S., F.R.C.S.
Professor J. A. Ryle, M.D., F.R.C.P. (*until April*, 1943).
P. Jenner Verrall, M.B., F.R.C.S. (*until January*, 1942).
Surgeon Rear-Admiral Sir Cecil Wakeley, K.B.E., C.B., D.Sc., F.R.C.S. (*from January*, 1942).
Sir Reginald Watson-Jones, M.Ch., F.R.C.S.
Colonel J. M. Weddell, C.B.E., F.R.C.S., *late* R.A.M.C. (*until November*, 1942).
The late Professor W. W. C. Topley, M.D., F.R.C.P., F.R.S. (*Joint Secretary until July*, 1941).
F. H. K. Green, M.D., F.R.C.P. (*Joint Secretary until July*, 1941 ; *Secretary from July*, 1941).

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Additional Members of Sub-Committees

Anaerobic Wound Infections ("*Anaerobes Sub-Committee*")—(*Chairman :* Major-General L. T. Poole, D.S.O., M.C., K.H.P., *late* R.A.M.C.).
Professor R. V. Christie, D.Sc., M.D., F.R.C.P. (*from April,* 1944).
Sir Percival Hartley, C.B.E., M.C., D.Sc., F.R.S.
W. E. van Heyningen, Ph. D.
Professor A. A. Miles, F.R.C.P.
Miss Muriel Robertson, D.Sc., F.R.S.
B. W. Williams, M.B., F.R.C.S.
Miss Marjorie G. Macfarlane, D.Sc., Ph.D. (*Secretary*).

Burns—(*Chairman :* Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P. ; *Secretary :* F. H. K. Green, M.D., F.R.C.P.).
R. B. Bourdillon, C.B.E., M.C., A.F.C., D.M.
Professor G. R. Cameron, D.Sc., F.R.C.P., F.R.S.
W. E. Chiesman, M.D., F.R.C.P.
A. M. Clark, M.C., Ch.M., F.R.F.P.S.
D. P. Cuthbertson, M.D., D.Sc.
Surgeon Captain A. Fairley, M.B., R.N.
Sir Harold Gillies, C.B.E., F.R.C.S.
Sir Archibald McIndoe, C.B.E., M.Sc., M.S., F.R.C.S.
F. J. McQuillin, B.Sc., D.Phil.
Professor R. A. Peters, M.C., M.D., F.R.S.
L. T. D. Williams, B.Sc., A.R.C.S.
Professor W. C. Wilson, M.B., F.R.C.S.E.

Chest Injuries—(*Chairman :* The late A. Tudor Edwards, M.D., F.R.C.S.).
P. R. Allison, Ch.M., B.Sc., F.R.C.S.
Surgeon Captain W. D. W. Brooks, B.M., F.R.C.S., R.N.
Clifford Hoyle, M.D., F.R.C.P.
Geoffrey Marshall, O.B.E., M.D., F.R.C.P.
T. Holmes Sellors, D.M., M.Ch., F.R.C.S.
O. S. Tubbs, M.B., F.R.C.S.
N. R. Barrett, M.Ch., F.R.C.S. (*Secretary*).

Crush Injuries (*Jointly with Traumatic Shock Committee*)—(*Chairman :* Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P.).
R. T. Grant, O.B.E., M.D., M.R.C.P., F.R.S.
Professor J. McMichael, M.D., F.R.C.P.E. (*Secretary*).

Pathological Specimens—(*Chairman :* Surgeon Rear-Admiral Sir Gordon Gordon-Taylor, K.B.E., C.B., M.S., F.R.C.S. ; *Secretary :* F. H. K. Green, M.D., F.R.C.P.).
Professor W. G. Barnard, F.R.C.P.
Professor G. R. Cameron, D.Sc., F.R.C.P., F.R.S.
Professor G. Hadfield, M.D., F.R.C.P.
L. W. Proger, M.R.C.S., L.R.C.P.
Professor M. J. Stewart, M.B., F.R.C.P.
Miss Joan M. Ross, M.D. (*Secretary of a special sub-committee on photographs and drawings*).

Vascular Injuries—(*Chairman :* Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P. ; *Secretary :* F. H. K. Green, M.D., F.R.C.P.).
The late Sir Thomas Lewis, C.B.E., M.D., F.R.C.P., F.R.S. (*Chairman until his death in March,* 1945).
Air Commodore Sir Stanford Cade, K.B.E., C.B., F.R.C.S., R.A.F.V.R.
Sol M. Cohen, F.R.C.S.
Professor J. H. Gaddum, Sc. D., M.R.C.S., F.R.S.
Major D. L. Griffiths, M.B.E., M.B., F.R.C.S.
B. C. Maybury, M.B., F.R.C.S.
Professor Dorothy S. Russell, M.D., Sc.D., M.R.C.P.
E. D. Telford, M.Sc., F.R.C.S.

Air-Raid Casualties

(*Jointly with the Ministry of Home Security and the Ministry of Health*)

Sir Claude Frankau, C.B.E., D.S.O., M.S., F.R.C.S. (*Chairman*).
Professor W. G. Barnard, F.R.C.P.
Professor J. D. Bernal, D.Sc., F.R.S.
Professor G. R. Cameron, D.Sc., F.R.C.P., F.R.S. (*until November,* 1940).
Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P.
Professor G. Hadfield, M.D., F.R.C.P.
Professor A. Bradford Hill, D.Sc., Ph.D.

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The late Professor B. A. McSwiney, Sc.D., M.B., F.R.S.
Professor S. Nevin, M.B., B.Sc., F.R.C.P.
A. Sandison, O.B.E., M.D.
Professor M. J. Stewart, M.B., F.R.C.P.
Professor S. Zuckerman, C.B., M.D., D.Sc., F.R.S.
A. N. Drury, C.B.E., M.D., F.R.S. (*Secretary*).
F. J. C. Herrald, M.B., M.R.C.P.E. (*Assistant Secretary*).

Brain Injuries

Professor E. D. Adrian, O.M., M.D., F.R.C.P., F.R.S. (*Chairman*).
Professor F. C. Bartlett, C.B.E., M.A., F.R.S.
Brigadier Sir Hugh Cairns, K.B.E., D.M., F.R.C.S., *late* R.A.M.C.
Surgeon Captain M. Critchley, M.D., F.R.C.P., R.N.V.R.
Norman M. Dott, M.B., F.R.C.S.E.
J. G. Greenfield, M.D., B.Sc., F.R.C.P.
Professor G. Jefferson, C.B.E., M.S., F.R.C.S.
Professor Aubrey J. Lewis, M.D., F.R.C.P.
J. F. E. Prideaux, C.B.E., M.R.C.S., L.R.C.P.
Brigadier G. Riddoch, M.D., F.R.C.P., *late* R.A.M.C.
Air Vice-Marshal Sir Charles P. Symonds, K.B.E., C.B., M.D., F.R.C.P., R.A.F.V.R.
F. M. R. Walshe, O.B.E., M.D., D.Sc., F.R.C.P., F.R.S.
E. A. Carmichael, C.B.E., M.B., F.R.C.P. (*Secretary until October*, 1942).
F. J. C. Herrald, M.B., M.R.C.P.E. (*Secretary from October*, 1942).

Nerve Injuries

Brigadier G. Riddoch, M.D., F.R.C.P., *late* R.A.M.C. (*Chairman*).
Brigadier W. R. Bristow, M.B., F.R.C.S., *late* R.A.M.C.
G. L. Brown, C.B.E., M.Sc., M.B., F.R.S. (*until May*, 1943).
Brigadier Sir Hugh Cairns, K.B.E., D.M., F.R.C.S., *late* R.A.M.C.
Professor W. E. le Gros Clark, D.Sc., F.R.C.S., F.R.S. (*from November*, 1943).
Surgeon Captain M. Critchley, M.D., F.R.C.P., R.N.V.R.
J. G. Greenfield, M.D., B.Sc., F.R.C.P.
Professor G. Jefferson, C.B.E., M.B., F.R.C.S. (*from October*, 1943).
Professor J. R. Learmonth, C.B.E., Ch.M., F.R.C.S.E.
Professor H. Platt, M.D., M.S., F.R.C.S.
Professor H. J. Seddon, D.M., F.R.C.S.
Air Vice-Marshal Sir Charles Symonds, K.B.E., C.B., M.D., F.R.C.P., R.A.F.V.R.
Professor J. Z. Young, M.A.
E. A. Carmichael, C.B.E., M.B., F.R.C.P. (*Secretary until September*, 1942).
F. J. C. Herrald, M.B., M.R.C.P.E. (*Secretary from September*, 1942).

Traumatic Shock

Professor G. E. Gask, C.M.G., D.S.O., F.R.C.S. (*Chairman until February*, 1940).
A. N. Drury, C.B.E., M.D., F.R.S. (*Chairman from February*, 1940 *until March*, 1943).
Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P. (*Chairman from March*, 1943).
G. L. Brown, M.Sc., M.B., F.R.S.
Professor G. R. Cameron, D.Sc., M.B., F.R.C.P., F.R.S.
Sir Henry H. Dale, O.M., G.B.E., M.D., F.R.C.P., F.R.S.
Professor Sir Howard Florey, M.B., Ph.D., F.R.S.
Sir Claude Frankau, C.B.E., D.S.O., M.S., F.R.C.S.
Professor J. H. Gaddum, Sc.D., M.R.C.S., F.R.S.
R. T. Grant, O.B.E., M.D., M.R.C.P., F.R.S.
Professor H. N. Green, M.Sc., M.D. (*from February*, 1944).
F. W. Holdsworth, M.Ch., F.R.C.S.
Surgeon Commander W. A. Hopkins, O.B.E., M.D., M.R.C.P.I., R.N. (*until January*, 1945).
Surgeon Commander N. M. McArthur, M.D., R.N. (*from January*, 1945).
Air Commodore R. R. Macintosh, D.M., F.R.C.S.E., D.A., R.A.F.V.R.
Professor J. McMichael, M.D., F.R.C.P.E.
Professor G. W. Pickering, M.B., F.R.C.P.
V. H. Riddell, M.D., F.R.C.S.
Professor J. A. Ryle, M.D., F.R.C.P. (*until April*, 1943).
Brigadier Sir Lionel Whitby, C.V.O., M.C., M.D., F.R.C.P., *late* R.A.M.C.
Professor W. C. Wilson, M.B., F.R.C.S.E.
Professor Sir Francis Fraser, M.D., F.R.C.P. (*Joint Secretary until September*, 1943).
The late Professor B. A. McSwiney, Sc.D., M.B., F.R.S. (*Joint Secretary until September*, 1943).
D. P. Cuthbertson, D.Sc., M.D. (*Secretary from September*, 1943).

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Additional Members of Sub-Committee

Anaesthetics—
J. Blomfield, O.B.E., M.D. (*Chairman*).
Brigadier A. S. Daly, F.R.C.S., D.A., *late* R.A.M.C.
C. Langton Hewer, M.B., D.A.
I. W. Magill, C.V.O., M.B., D.A.
M. D. Nosworthy, M.D., D.A.
G. S. W. Organe, M.D., D.A. (*Secretary*).

Malaria

Major-General Sir Alexander Biggam, K.B.E., C.B., M.D., F.R.C.P., *late* R.A.M.C. (*Chairman*).
Professor J. H. Burn, M.D., F.R.S.
Professor P. A. Buxton, C.M.G., M.R.C.S., F.R.S.
Sir Rickard Christophers, C.I.E., O.B.E., M.B., F.R.S.
Brigadier F. A. E. Crew, M.D., D.Sc., F.R.S., *late* R.A.M.C.
Professor T. H. Davey, O.B.E., M.D.
Professor E. C. Dodds, M.V.O., M.D., F.R.C.P., F.R.S.
Surgeon Vice-Admiral Sir Sheldon Dudley, K.C.B., O.B.E., M.D., F.R.C.P., F.R.S., K.H.P.
Professor J. H. Gaddum, Sc.D., M.R.C.S., F.R.S.
The late Colonel S. P. James, C.S.I., C.M.G., M.D., F.R.S., I.M.S. (*retd.*).
W. H. Kauntze, C.M.G., M.B.E., M.D., F.R.C.P.
H. King, D.Sc., F.R.S.
Lieut.-Colonel B. G. Maegraith, M.B., B.Sc., D.Phil., R.A.M.C.
Major-General L. T. Poole, D.S.O., M.C., K.H.P., *late* R.A.M.C.
Brigadier J. A. Sinton, V.C., O.B.E., D.Sc., M.B., *late* R.A.M.C.
P. G. Stock, C.B., C.B.E., M.B., F.R.C.P.
Air Marshal Sir Harold Whittingham, K.C.B., K.B.E., F.R.C.P., K.H.P., R.A.F.
Professor L. J. Witts, M.D., F.R.C.P.
Major J. W. Howie, M.D., R.A.M.C.
F. Hawking, D.M., D.T.M. (*Secretary*).
Major J. Reid, M.B., M.R.C.P., R.A.M.C. (*Assistant Secretary*).

Additional Members of Sub-Committees

Chemistry and Pharmacology—(*Chairman :* H. King, D.Sc., F.R.S. ; *Secretary :* F. Hawking, D.M., D.T.M.).
S. Ellingworth.
D. Ll. Hammick.
Professor E. J. King, Ph.D.
Surgeon Commander G. Southwell-Sander, M.B., D.P.H., R.N.

Drug Prophylaxis—(*Chairman :* Major-General Sir Alexander Biggam, K.B.E., C.B., M.D., F.R.C.P., *late* R.A.M.C. ; *Secretary :* F. Hawking, D.M., D.T.M.).
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Colonel C. S. Ryles.
Surgeon Commander G. Southwell-Sander, M.B., D.P.H., R.N.
P. G. Shute.

Therapy—(*Chairman :* Major-General Sir Alexander Biggam, K.B.E., C.B., M.D., F.R.C.P., *late* R.A.M.C. ; *Secretary :* F. Hawking, D.M., D.T.M. ; *Assistant Secretary :* Major J. Reid, M.B., M.R.C.P.).
Surgeon Commander G. Southwell-Sander, M.B., D.P.H., R.N.

Typhus

Major-General L. T. Poole, C.B., D.S.O., M.C., M.B., K.H.P., *late* R.A.M.C. (*Chairman*).
C. H. Andrewes, M.D., F.R.C.P., F.R.S.
Professor S. P. Bedson, M.D., M.Sc., F.R.C.P., F.R.S.
Lieut.-Colonel H. J. Bensted, O.B.E., M.C., M.R.C.S., R.A.M.C.
Major-General Sir Alexander Biggam, K.B.E., C.B., M.D., F.R.C.P., *late* R.A.M.C.
Professor P. A. Buxton, C.M.G., M.R.C.S., F.R.S.
Surgeon Commander D. Duncan, O.B.E., M.D., D.P.H., R.N.
Professor M. van den Ende, M.B., Ph. D.
A. Felix, D.Sc., F.R.S.
R. Lewthwaite, D.M., M.R.C.P.
M. D. Mackenzie, M.D., D.P.H.
Major K. Mellanby, Ph. D.
Major-General D. T. Richardson, C.B., M.C., M.B., K.H.S., *late* R.A.M.C.
Air Marshal Sir Harold Whittingham, K.C.B., K.B.E., F.R.C.P., K.H.P., R.A.F.
F. Fulton, D.M. (*Secretary*).

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Jaundice

Professor L. J. Witts, M.D., F.R.C.P. (*Chairman*).
Professor S. P. Bedson, M.D., F.R.S.
Major-General Sir Alexander Biggam, K.B.E., C.B., M.D., F.R.C.P., *late* R.A.M.C.
W. H. Bradley, D.M.
A. N. Drury, C.B.E., M.D., F.R.S.
Lieut.-Colonel J. E. Gordon, M.D., M.C.A.U.S.
F. O. MacCallum, M.D.
Professor J. McMichael, M.D., F.R.C.P.E.
Brigadier T. E. Osmond, M.B., *late* R.A.M.C.
Major-General L. T. Poole, D.S.O., M.C., K.H.P., *late* R.A.M.C.
Professor W. J. Tulloch, O.B.E., M.D.
Professor G. S. Wilson, M.D., F.R.C.P., K.H.P.
A. M. McFarlan, M.B. (*Secretary*).

Tuberculosis in Wartime

The late Viscount Dawson of Penn, P.C., G.C.V.O., K.C.B., M.D., F.R.C.P. (*Chairman*).
T. Stenner Evans, M.B., D.P.H.
Professor M. Greenwood, D.Sc., F.R.C.P., F.R.S.
F. R. G. Heaf, M.D., M.R.C.P.
The late G. G. Kayne, M.D., M.R.C.P., D.P.H.
Colonel Sir Alexander Russell, C.B.E., M.D., D.P.H., I.M.S. (*retd.*).
Miss May Smith, D.Sc.
Norman F. Smith, D.M.
Wing-Commander R. R. Trail, M.C., M.D., F.R.C.P., R.A.F.V.R.
Professor G. S. Wilson, M.D., F.R.C.P., D.P.H., K.H.P.
P. D'Arcy Hart, M.D., F.R.C.P. (*Secretary*).

Additional Members of Sub-Committee

Mass Radiography—(*Secretary :* P. D'Arcy Hart, M.D., F.R.C.P.).
S. Cochrane Shanks, M.D., F.R.C.P., F.F.R. (*Chairman*).
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W. H. Coldwell, M.B., D.M.R.E., F.F.R.
Major P. Kerley, M.D., F.R.C.P., D.M.R.E., F.F.R., R.A.M.C.
Brigadier D. B. McGrigor, O.B.E., M.B., D.M.R.E., *late* R.A.M.C.
Lieutenant G. B. Stanford, M.R.C.S., D.M.R.E., F.R.P.S., R.A.M.C.

Bed-Bug Infestation

The late Sir John C. G. Ledingham, C.M.G., D.Sc., F.R.C.P., F.R.S. (*Chairman*).
S. A. Ashmore, B.Sc., F.I.C.
Professor P.A. Buxton, C.M.G., M.R.C.S., F.R.S.
Professor G. R. Cameron, D.Sc., F.R.C.P., F.R.S.
Colonel W. C. Gunn, M.D., D.P.H., R.A.M.C. (*retd.*).
H. Symon.
J. Macmillan, D.S.O., M.C., M.B., D.P.H.
G. W. Monier-Williams, O.B.E., M.C., Ph.D., F.I.C.
Professor J. W. Munro, D.Sc.
R. E. Stradling, C.B., M.C., D.Sc., Ph.D., M.Inst.C.E.
P. G. Stock, C.B., C.B.E., M.B., F.R.C.P.
A. W. McKenny-Hughes, D.I.C., F.R.E.S. (*Secretary*).

Therapeutic Requirements

Professor L. J. Witts, M.D., F.R.C.P. (*Chairman*).
Professor J. H. Burn, M.D., F.R.S.
The late Professor A. J. Clark, M.C., M.D. F.R.C.P. F.R.S.
C. E. Corfield, B.Sc., F.I.C., Ph.C.
H. Davis, B.Sc., Ph.D.
Professor J. A. Gunn, M.D., D.Sc., F.R.C.P.
P. Hamill, M.D., D.Sc., F.R.C.P.
R. D. Hutchinson, M.P.S.
J. M. Johnston, M.D., F.R.C.S.E.
W. P. Kennedy, B.Sc., Ph.D., L.R.C.P. & S.E.
A. Mortimer, O.B.E.
A. W. Thompson, M.B.E.
Professor G. H. Wooldridge, F.R.C.V.S.
C. H. Hampshire, M.B., B.Sc., Ph.C., F.R.I.C. (*Secretary*).

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Chemotherapy

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C. R. Harington, Ph.D., F.R.S. (*Chairman from February*, 1945).
Professor C. H. Browning, M.D., F.R.S. (*until February*, 1945).
Professor J. H. Burn, M.D., F.R.S.
Sir Rickard Christophers, C.I.E., O.B.E., M.B., F.R.S. (*until February*, 1945).
L. Colebrook, M.B., F.R.C.O.G., F.R.S. (*until February*, 1945).
A. N. Drury, C.B.E., M.D., F.R.S. (*from February*, 1945).
Professor Sir Howard Florey, M.B., Ph.D., F.R.S. (*from February*, 1945).
P. D'Arcy Hart, M.D., F.R.C.P. (*from February*, 1945).
The late Colonel S. P. James, C.S.I., C.M.G., M.D., F.R.S., I.M.S. (*retd.*).
Professor D. Keilin, Sc.D., F.R.S.
A. A. Miles, F.R.C.P. (*from February*, 1945).
Professor Sir Robert Robinson, D.Sc., P.R.S.
G. S. Whitby, D.Sc., Ph.D. (*March*, 1942 *to February*, 1945).
C. H. Andrewes, M.D., F.R.C.P., F.R.S. (*General Secretary until February*, 1945).
H. King, D.Sc., F.R.S. (*Chemical Secretary until February*, 1945).
F. Hawking, D.M., D.T.M. (*Biological Secretary from February*, 1945).
J. Walker, Ph.D., D.Phil. (*Chemical Secretary from February*, 1945).

Chemotherapy of Malaria (jointly with Malaria Committee)

C. R. Harington, Ph.D., F.R.S. (*Chairman*).
Professor J. H. Gaddum, Sc.D., F.R.S.
Professor D. Keilin, Sc.D., F.R.S.
H. King, D.Sc., F.R.S.
Professor Sir Robert Robinson, D.Sc., P.R.S.
F. Hawking, D.M., D.T.M. (*Joint Secretary*).
Major J. Reid, M.B., M.R.C.P., R.A.M.C. (*Joint Secretary*).

Penicillin Clinical Trials

Professor H. R. Dean, M.D., F.R.C.P. (*Chairman*).
Professor J. H. Burn, M.D., F.R.S.
A. N. Drury, C.B.E., M.D., F.R.S.
Surgeon Vice-Admiral Sir Sheldon Dudley, K.C.B., O.B.E., M.D., F.R.C.P., F.R.S., K.H.P.
Professor Sir Alexander Fleming, M.B., F.R.C.S., F.R.C.P., F.R.S.
Professor Sir Howard Florey, M.B., Ph.D., F.R.S.
Sir Archibald Gray, C.B.E., M.D., F.R.C.P., F.R.C.S.
C. H. Hampshire, M.B., B.Sc., Ph.C., F.R.I.C.
Sir Percival Hartley, C.B.E., M.C., D.Sc., F.R.S.
R. Vaughan Hudson, F.R.C.S.
Air Vice-Marshal G. L. Keynes, M.D., F.R.C.S., R.A.F.V.R.
Professor J. R. Learmonth, C.B.E., Ch.M., F.R.C.S.E.
Major-General L. T. Poole, D.S.O., M.C., K.H.P., *late* R.A.M.C.
C. M. Scott, D.Sc., M.B.
J. W. Trevan, M.B., B.Sc., F.R.C.S., F.R.S.
Professor R. V. Christie, D.Sc., M.D., F.R.C.P. (*Secretary*).
Professor L. P. Garrod, M.D., F.R.C.P. (*Assistant Secretary*).

Penicillin Synthesis

Professor Sir Robert Robinson, D.Sc., P.R.S. (*Chairman*).
W. Bradley, M.Sc., Ph.D.
H. C. Carrington, M.Sc., Ph.D.
E. Chain, Ph.D.
A. H. Cook, B.Sc., Ph.D.
C. R. Harington, Ph.D., F.R.S.
Professor I. M. Heilbron, D.S.O., D.Sc., F.R.S.
A. Mortimer, O.B.E.
G. Newbury, B.Sc., F.R.I.C.
D. A. Peak, M.Sc., D.Phil.
F. A. Robinson, M.Sc., F.R.I.C.
W. A. Sexton, B.Sc., Ph.D., F.R.I.C.
S. Smith, B.Sc., Ph.D., F.R.I.C.
Professor A. R. Todd, B.Sc., Ph.D., F.R.S.
H. King, D.Sc., F.R.S. (*Secretary*).

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Care of Shipwrecked Personnel

Surgeon Vice-Admiral Sir Sheldon Dudley, K.C.B., O.B.E., M.D., F.R.C.P., F.R.S. K.H.P. (*Chairman*).
Surgeon-Captain M. Critchley, M.D., F.R.C.P., R.N.V.R.
A. N. Drury, C.B.E., M.D., F.R.S.
Surgeon Captain M. Critchley, M.D., F.R.C.P., R.N.V.R.
Surgeon Commander R. A. Graff, M.R.C.S., L.R.C.P., R.N.
The late Sir Thomas Lewis, C.B.E., M.D., F.R.C.P., F.R.S.
Professor R. A. McCance, M.D., Ph.D., F.R.C.P.
Air Commodore T. McClurkin, M.B., B.Ch., R.A.F.
Wing Commander T. F. Macrae, O.B.E., D.Sc., R.A.F.V.R.
Spencer Nairne, M.R.C.S., L.R.C.P.
Captain R. Oliver-Bellasis, C.V.O., R.N.
Professor B. S. Platt, C.M.G., M.Sc., M.B., Ph.D. (*Secretary*).

Haemoglobin Surveys

A. N. Drury, C.B.E., M.D., F.R.S. (*Chairman*).
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C. R. Harington, Ph.D., F.R.S.
Professor A. Bradford Hill, D.Sc., Ph.D.,
Miss Helen M. M. Mackay, M.D., F.R.C.P.
H. E. Magee, D.Sc., M.B.
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A. P. Meiklejohn, B.M., B.Sc.
Hugh H. Smith, M.D.
Professor V. P. Sydenstricker, M.D.
Miss Janet M. Vaughan, O.B.E., D.M., F.R.C.P.
Miss Lucy Wills, M.B., B.S.
Professor G. Payling Wright, D.M., F.R.C.P.
P. L. Mollison, M.B., M.R.C.P. (*Secretary until August*, 1943).
D. P. Cuthbertson, D.Sc., M.D. (*Secretary from August*, 1943).

Accessory Food Factors

(*Jointly with the Lister Institute of Preventive Medicine*)

Sir Edward Mellanby, K.C.B., M.D., Sc.D., F.R.C.P., F.R.S. (*Chairman until March*, 1943).
Professor R. A. Peters, M.C., M.D., F.R.S. (*Chairman from March*, 1943).
Miss K. H. Coward, D.Sc.
J. M. Hamill, O.B.E., M.D., D.Sc. (*until* 1940).
Miss E. M. Hume, M.A.
Wing Commander T. F. Macrae, O.B.E., D.Sc., R.A.F.V.R.
H. E. Magee, D.Sc., M.B.
Professor R. A. McCance, M.D., Ph.D., F.R.C.P.
Professor B. S. Platt, C.M.G., M.Sc., M.B., Ph.D.
O. Rosenheim, D.Sc., F.R.S.
S. S. Zilva, D.Sc., Ph.D., F.R.I.C.
Miss H. Chick, C.B.E., D.Sc. (*Secretary*).

Additional Members of Sub-Committees

Vitamin A—(*Secretary :* Miss E. M. Hume, M.A.).
Professor R. A. Morton, D.Sc., Ph.D. (*Chairman*).
Sir Jack Drummond, D.Sc., F.R.S.
S. K. Kon, D.Sc., Ph.D.
T. Moore, D.Sc., Ph.D.
Mrs. I. Smedley-MacLean, D.Sc., F.R.I.C.

Vitamin B—(*Chairman :* Professor R. A. Peters, M.C., M.D., F.R.S.
Secretary : Wing Commander T. F. Macrae, O.B.E., D.Sc., R.A.F.V.R.).
Miss A. M. Copping, M.Sc.
L. J. Harris, Sc.D., D.Sc., Ph.D.. F.R.I.C.
S. K. Kon, D.Sc., Ph.D.
R. A. Webb, D.Phil.

Vitamin C—(*Chairman :* Professor R. A. Peters, M.C., M.D., F.R.S.).
L. W. Mapson, Ph.D.
Professor Sir Leonard G. Parsons, M.D., F.R.C.P., F.R.C.O.G.
Professor J. C. Spence, M.C., M.D., F.R.C.P.
J. R. P. O'Brien, B.M., B.Ch. (*Secretary*).

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T. A. Webster, A.I.C.
S. K. Kon, D.Sc., Ph.D.
A. A. Miles, F.R.C.P.
Professor R. A. Morton, D.Sc., Ph.D.

Vitamin E—(*Secretary :* Miss E. M. Hume, M.A.).
Miss A. M. Copping, M.Sc.
Sir Jack Drummond, D.Sc., F.R.S.
T. Moore, D.Sc., Ph.D.
Professor R. A. Morton, D.Sc., Ph.D.
Professor A. R. Todd, B.Sc., Ph.D., F.R.S.

Vitamin Claims—(*Chairman :* Professor R. A. Peters, M.C., M.D., F.R.S.; *Secretary :* Miss K. H. Coward, D.Sc.).
G. A. Adams.
P. N. R. Butcher.
Sir Jack Drummond, D.Sc., F.R.S.
L. J. Harris, Sc.D., D.Sc., Ph.D., F.R.I.C.
Professor H. P. Himsworth, M.D., F.R.C.P.
H. Jephcott.

Goitre—
Professor S. J. Cowell, M.B., F.R.C.P. (*Chairman*).
C. R. Harington, Ph.D., F.R.S.
F. C. Kelly, Ph.D., B.Sc.
Professor J. A. Ryle, M.D., F.R.C.P.
Mrs. Dagmar C. Wilson, M.D., M.R.C.P., F.R.C.O.G.
Miss Margaret M. Murray, D.Sc. (*Secretary*).

Post-war Opportunities for Nutritional Research in Occupied Countries in Europe—(*Chairman :* Professor R. A. Peters, M.C., M.D., F.R.S. : *Secretary :* Miss H. Chick, C.B.E., D.Sc.).
Professor H. P. Himsworth, M.D., F.R.C.P.
A. P. Meiklejohn, B.M., B.Sc.
H. M. Sinclair, D.M., B.Sc.

Food Rationing: Special Diets

(An advisory committee appointed at the request of the Ministry of Food, Ministry of Health, and Department of Health for Scotland)

Sir Edward Mellanby, K.C.B., M.D., Sc.D., F.R.C.P., F.R.S. (*Chairman*).
Professor L. S. P. Davidson, M.D., F.R.C.P.E.
The late Viscount Dawson of Penn, P.C., G.C.V.O., K.C.B., M.D., F.R.C.P.
Professor Sir Francis Fraser, M.D., F.R.C.P.
The Rt. Hon. Lord Horder, G.C.V.O., M.D., F.R.C.P.
R. D. Lawrence, M.D., F.R.C.P.
Professor R. A. McCance, M.D., Ph.D., F.R.C.P.
Professor J. C. Spence, M.C., M.D., F.R.C.P.
Professor H. P. Himsworth, M.D., F.R.C.P. (*Secretary*).

Protein Requirements

Professor H. P. Himsworth, M.D., F.R.C.P. (*Chairman*).
Professor A. C. Chibnall, Sc.D., F.R.S.
Professor S. J. Cowell, M.B., F.R.C.P.
R. Cruickshank, M.D., F.R.C.P.
C. R. Harington, Ph.D., F.R.S.
Professor R. A. McCance, M.D., Ph.D., F.R.C.P.
A. Neuberger, M.D., Ph.D.
Professor R. A. Peters, M.C., M.D., F.R.S.
Professor B. S. Platt, C.M.G., M.Sc., M.B., Ph.D.
Professor F. G. Young, D.Sc., Ph.D.
D. P. Cuthbertson, D.Sc., M.D. (*Secretary*).

Drying of Human Milk

A. N. Drury, C.B.E., M.D., F.R.S. (*Chairman*).
G. I. Brodie, M.B., D.P.H.
S. K. Kon, D.Sc., Ph.D.
A. S. McFarlane, M.B., B.Sc.
Professor A. A. Moncrieff, M.D., F.R.C.P.
A. L. Walker, M.B., F.R.C.S., F.R.C.O.G.
Professor G. S. Wilson, M.D., F.R.C.P., D.P.H., K.H.P.
Miss Joyce Wright, D.M.
F. J. C. Herrald, M.B., M.R.C.P.E. (*Secretary*).

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Military Personnel Research Committee

*The Right Hon. Viscount Falmouth (*Chairman*).
Professor F. C. Bartlett, C.B.E., M.A., F.R.S.
Senior Controller M. Baxter-Ellis, C.B.E. (*from November*, 1943).
*G. L. Brown, C.B.E., M.Sc., M.B., F.R.S.
Brigadier A. D. Buchanan-Smith (*since May*, 1943).
*Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P.
Wing Commander C. E. Chilton, R.A.F. (*April to November*, 1941).
*The late K. J. W. Craik, Ph.D.
Brigadier F. A. E. Crew, M.D., D.Sc., F.R.S., *late* R.A.M.C.
Surgeon Vice-Admiral Sir Sheldon Dudley, K.C.B., O.B.E., M.D., F.R.C.P., F.R.S., K.H.P.
Major General A. R. Godwin-Austen, C.B., O.B.E., M.C. (*April*, 1943 *to January*, 1944).
H. J. Gough, C.B., M.B.E., D.Sc., Ph.D., M.I.Mech.E., F.R.S.
*C. S. Hallpike, M.B., F.R.C.P., F.R.C.S.
Lieutenant-General Sir Alexander Hood, G.B.E., K.C.B., M.D., F.R.C.P., K.H.P., *late* R.A.M.C.
*The Right Hon. Lord Horder, G.C.V.O., M.D., F.R.C.P.
*Brigadier C. G. Ling, C.B., D.S.O., M.C.
*Sir John Parsons, C.B.E., D.Sc., M.B., F.R.C.S., F.R.S.
Major-General D. T. Richardson, C.B., M.C., M.B., K.H.S., *late* R.A.M.C.
Major-General S. F. Rowell, C.B.E. (*from January*, 1944).
*Professor G. I. Taylor, M.C., D.Sc., F.R.S. (*until January*, 1943).
*Major-General Sir Henry L. Tidy, K.B.E., M.D., F.R.C.P.
Wing Commander D. J. Waghorn, A.F.C., R.A.F. (*from November*, 1941).
*Kenneth M. Walker, O.B.E., M.B., F.R.C.S.
Chief Controller L. V. L. E. Whately, C.B.E. (*until November*, 1943).
Air Marshal Sir Harold Whittingham, K.C.B., K.B.E., F.R.C.P., K.H.P., R.A.F.
*E. A. Carmichael, C.B.E., M.B., F.R.C.P. (*Secretary*).

Additional Members of Sub-Committees

Accidents to Army Vehicles—(*Chairman :* Professor F. C. Bartlett, C.B.E., M.A., F.R.S.).
Colonel E. R. Cawdron (*until November*, 1942).
Lieut.-Colonel F. N. Charlton (*from November*, 1942).
Major L. Cromwell (*from August to November*, 1942).
Professor A. Bradford Hill, D.Sc., Ph.D.
Lieut.-Colonel E. V. Hill (*from November*, 1943).
Brigadier K. G. McLean (*until November*, 1943).
Major W. J. Potter (*until August*, 1942).
Lieut.-Colonel J. W. A. Stones (*until November*, 1943).
F. J. C. Herrald, M.B., M.R.C.P.E. (*Secretary*).

Air-borne Troops—(*Chairman :* E. A. Carmichael, C.B.E., M.B., F.R.C.P. ; *Secretary :* G. L. Brown, C.B.E., M.Sc., M.B., F.R.S.).
T. Bedford, D.Sc., Ph.D.
Captain W. B. P. Bradish.
Major D. C. Curme.
Brigadier A. A. Eagger, C.B.E., M.B., Ch.B., *late* R.A.M.C.
Captain J. W. Magladery, M.D., R.C.A.M.C. (*from February*, 1942).
Sir Edward Penton, K.B.E., B.Sc., F.I.C.
Sir Robert Pickard, D.Sc., F.R.S.
Major M. D. Sieff.
Lieut.-Colonel K. B. Smyth.
J. W. Thomas.
B. H. Wilsdon, B.Sc.
Flight Lieutenant B. J. O. Winfield, R.A.F.V.R.
Wing Commander R. H. Winfield, R.A.F.O.

Armoured Fighting Vehicles—(*Chairman :* Sir Edward Mellanby, K.C.B., M.D., Sc.D., F.R.C.P., F.R.S. ; *Secretary :* E. A. Carmichael, C.B.E., M.B., F.R.C.P.).
T. Bedford, D.Sc., Ph.D.
Brigadier W. M. Blagden (*from July*, 1943).
Colonel J. A. M. Bond (*until September*, 1941).
Colonel G. W. Busk (*from December*, 1942).
Lieut.-Colonel A. C. Campbell, R.A.M.C. (*January*, 1942 *to October*, 1943).
Lieut.-Colonel P. J. L. Capon, M.R.C.S., D.P.H., R.A.M.C. (*from October*, 1943).
Lieut.-Colonel D. H. Carter (*from December*, 1943).
Professor I. de Burgh Daly, M.D., F.R.S. (*from March*, 1943).

* Members of original Body Protection Committee (p. 135).

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Professor C. A. Lovatt Evans, D.Sc., F.R.C.P., F.R.S.
Brigadier M. L. Formby, M.B., B.Sc., F.R.C.S., *late* R.A.M.C. (*from March*, 1942).
Lieut.-Colonel G. Gaisford (*from January*, 1945).
Sir G. A. Harford (*from August*, 1942).
Lieut.-Colonel R. N. Harding-Newman (*December*, 1942 *to October*, 1944).
W. J. Mesher (*from December*, 1942).
Lieut.-Colonel V. R. Paravicini (*from October*, 1944).
E. E. Pochin, M.D., F.R.C.P.
Colonel E. McLeod Ross (*from February*, 1942).
Colonel D. M. Rycroft.
Colonel A. A. Sandiford, M.C., M.B., D.P.H., R.A.M.C.
O. M. Solandt, M.D., M.R.C.P.
Colonel C. W. M. Timmis, D.S.O. (*September*, 1941 *to December*, 1942).
F. A. Vick, Ph.D., F.Inst.P.

Body Armour and Helmets—(*Chairman :* Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P. ; *Secretary :* E. A. Carmichael, C.B.E., M.B., F.R.C.P.).
Professor J. D. Bernal, D.Sc., F.R.S.
Professor Sir Hugh Cairns, K.B.E., D.M., F.R.C.S. (*since April*, 1942).
W. A. Carter.
O. M. Solandt, M.D., M.R.C.P.
Professor S. Zuckerman, C.B., D.Sc., M.D., F.R.S.

Clothing—(*Chairman :* The Right Hon. Viscount Falmouth).
H. Bradley, B.Sc., D.I.C. (*from October*, 1941).
Commander G. T. Coney, R.N. (*until October*, 1941).
Professor C. G. Douglas, C.M.G., M.C., M.D., B.Sc., F.R.S.
R. M. Filmer, M.B.E., B.Sc., F.I.C. (*from October*, 1941).
Captain R. Oliver-Bellasis, C.V.O., R.N. (*from October*, 1941).
Sir Edward Penton, K.B.E., B.Sc., F.I.C. (*since August*, 1941).
Sir Robert Pickard, D.Sc., F.R.S.
Major M. D. Sieff.
J. R. Whinfield (*from March*, 1942).
Captain F. S. Wigley.
B. H. Wilsdon, B.Sc.,
T. Bedford, D.Sc., Ph.D. (*Secretary*).

Entomology—
Professor P. A. Buxton, C.M.G., M.R.C.S., F.R.S. (*Chairman*).
Major W. L. Aylwin (*until April*, 1942).
Major-General Sir Alexander Biggam, K.B.E., C.B., M.D., F.R.C.P., *late* R.A.M.C.
Sir Rickard Christophers, C.I.E., O.B.E., M.B., F.R.S. (*from September*, 1942).
Professor R. M. Gordon, O.B.E., M.D., Sc.D., F.R.C.P.
Air Commodore T. McClurkin, M.B., D.P.H., R.A.F.
Major K. Mellanby, Ph.D., R.A.M.C.
Professor J. W. Munro, D.F.C., D.Sc. (*from February*, 1943).
Major H. I. Pocock (*from April*, 1942).
V. B. Wigglesworth, M.D., F.R.S. (*Secretary*).

Motion Sickness—(*Chairman :* E. A. Carmichael, C.B.E., M.B., F.R.C.P. ; *Secretary :* G. L. Brown, C.B.E., M.Sc., M.B., F.R.S.).
Surgeon Captain R. A. Graff, M.R.C.S., L.R.C.P., R.N.
Brigadier R. J. Napier.
Major H. I. Pocock.
Professor L. J. Witts, M.D., F.R.C.P.

Rations—(*Chairman :* E. A. Carmichael, C.B.E., M.B., F.R.C.P.).
Major I. A. Anderson, M.B.E., B.Sc., M.B.
Major E. Barnard, C.B.E., D.S.O.
E. B. Hughes, D.Sc.
J. King.
L. H. Lampitt, D.Sc., F.R.I.C.
Professor R. A. McCance, M.D., Ph.D., F.R.C.P.
Wing Commander T. F. Macrae, O.B.E., D.Sc., R.A.F.V.R.
Brian B. Roberts, D.Sc.
Professor B. S. Platt, C.M.G., M.Sc., M.B., Ph.D. (*Secretary*).

Weapons (Biological Assay)—(*Secretary :* G. L. Brown, C.B.E., M.Sc., M.B., F.R.S.).
Sir Henry H. Dale, O.M., G.B.E., M.D., F.R.C.P., F.R.S. (*Chairman*).
Major W. H. Aylwin (*from November*, 1941).
Professor J. D. Bernal, D.Sc., F.R.S.
Major A. J. McAlpine Downie (*from November*, 1941).

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Surgeon Captain R. A. Graff, M.R.C.S., L.R.C.P., R.N.
Professor C. A. Lovatt Evans, D.Sc., F.R.C.P., F.R.S.
Brigadier J. L. P. Macnair.
A. H. T. Robb-Smith, M.D.
Professor S. Zuckerman, C.B., D.Sc., M.D., F.R.S.

Vision—(*Secretary :* E. A. Carmichael, C.B.E., M.B., F.R.C.P.).
Sir John H. Parsons, C.B.E., D.Sc., M.B., F.R.C.S., F.R.S. (*Chairman*).
Lieut.-Colonel H. E. C. de Chassiron.
Brigadier Sir Stewart Duke-Elder, K.C.V.O., M.D., Ph.D., F.R.C.S.
E. E. Pochin, M.D., F.R.C.P.
Major H. I. Pocock.
F. A. Vick, M.Sc., Ph.D., F.Inst.P.

Royal Naval Personnel Research Committee

Sir Edward Mellanby, K.C.B., M.D., Sc.D., F.R.C.P., F.R.S. (*Chairman*).
Captain J. R. S. Brown, R.N. (*October*, 1943 *to October*, 1944).
J. Buckingham.
Captain G. O. C. Davies, R.N. (*until March*, 1943 *and also from February*, 1945).
Surgeon Vice-Admiral Sir Sheldon Dudley, K.C.B., O.B.E., M.D., F.R.C.P., F.R.S., K.H.P.
Surgeon Captain R. A. Graff, M.R.C.S., L.R.C.P., R.N. (*from April*, 1945).
Surgeon Commander E. James, M.D., M.R.C.P.E., R.N. (*from April*, 1945).
Captain F. W. H. Jeans, R.N. (*March*, 1943 *to December*, 1944).
Captain R. Oliver-Bellasis, C.V.O., R.N. (*until March*, 1943).
Captain H. K. P. Oram, R.N. (*from March*, 1943).
Professor B. S. Platt, C.M.G., M.Sc. M.B., Ph.D.
Commander M. G. Rimington, D.S.O., R.N. (*from October*, 1944).
A. Rodger, M.A. (*from April*, 1945).
P. E. Vernon, Ph.D. (*until April*, 1945).
G. L. Brown, C.B.E., M.Sc., M.B., F.R.S. (*Secretary*).
Surgeon Lieutenant-Commander F. P. Ellis, O.B.E., M.B., R.N. (*Naval Medical Secretary from January*, 1944).

Additional Members of Sub-Committees

Clothing—
O. S. N. Richards (*Director of Victualling*), (*Chairman*).
T. Bedford, D.Sc., Ph.D.
R. B. Bourdillon, C.B.E., M.C., A.F.C., D.M.
F. Brookhouse.
J. C. D. Hutchinson, M.A.
O. M. Lidwell, D.Phil.
Commander H. C. Martell, R.N.
J. S. Weiner, M.Sc.
Lieutenant-Commander M. O. Pelton, R.N.V.R. (*Secretary*).

Gunnery—(*Secretary :* G. L. Brown, C.B.E., M.Sc., M.B., F.R.S.).
Commander (E) J. E. Golby, R.N. (*Chairman*).
Lieutentant-Commander P. R. Bird, R.N. (*until October*, 1944).
Lieutenant-Commander Sir Thomas Butler, Bt., R.N. (*October*, 1944 *to February*, 1945).
R. W. Cheshire.
Commander (E) A. B. Chibnall, R.N. (*January*, 1944 *to August*, 1944).
Professor W. E. le Gros Clark, D.Sc., F.R.C.S., F.R.S.
Lieutenant-Commander P. J. S. Hardinge, M.B.E., R.N. (*from February*, 1945).
Lieutenant-Commander P. J. Hill-Norton, R.N. (*August*, 1943 *to January*, 1945).
E. O. Lemon.
Commander (E) J. E. H. Machen, R.N. (*from August*, 1944).
Commander C. M. Parry, R.N. (*until August*, 1943).
Commander M. J. Ross, D.S.C., R.N. (*from August*, 1944).
Commander R. I. A. Sarell, D.S.O., R.N. (*from January*, 1945).
A. J. Sims, R.C.N.C.
Lieutenant-Commander C. E. J. Streatfeild, R.N. (*from February*, 1945).
Commander R. E. Washbourn, D.S.O., R.N. (*from November*, 1944).
A. G. M. Weddell, M.D., D.Sc.

Habitability—(*Secretary :* Surgeon Lieutenant-Commander F. P. Ellis, O.B.E., M.B., R.N.).
Surgeon Captain M. Critchley, M.D., F.R.C.P., R.N.V.R. (*Chairman*).
T. Bedford, D.Sc., Ph.D.
M. G. Bennett.

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R. C. Frederick.
Ezer Griffiths, D.Sc., F.R.S.
G. A. Knight.
B. McArdle, M.D., M.R.C.P.
N. H. Mackworth, M.B., Ch.B.
Commander R. I. A. Sarell, D.S.O., R.N.
A. J. Sims, R.C.N.C.
F. E. Smith (*from July*, 1945).
Surgeon Commander G. H. G. Southwell-Sander, M.B., B.Ch., R.N.

Underwater Physiology—(*Chairman and Secretary :* G. L. Brown, C.B.E., M.Sc., M.B., F.R.S.).
Surgeon Lieutenant-Commander W. M. Davidson, M.B., B.Ch., R.N. (*from October*, 1944).
Surgeon Lieutenant-Commander K. W. Donald, D.S.C., M.D., M.R.C.P., R.N.
Professor J. B. S. Haldane, M.A., F.R.S.
J. McAulay, D.Sc.
B. H. C. Matthews, C.B.E., Sc.D., F.R.S.
Surgeon Commander C. L. G. Pratt, O.B.E., M.D., M.Sc., R.N.V.R.
Commander W. O. Shelford, R.N.

Visual Problems—(*Secretary :* G. L. Brown, C.B.E., M.Sc., M.B., F.R.S.).
Surgeon Commander D. M. Beaton, O.B.E., R.N. (*Chairman*).
R. W. Cheshire.
Lieutenant-Commander M. O. Pelton, R.N.V.R.
E. E. Pochin, M.D., F.R.C.P.
Lieutenant-Commander T. E. F. Pooley, R.N.
Surgeon Lieutenant-Commander P. G. Rowsell, M.B., B.S., R.N.
W. S. Styles, Ph.D.
P. E. Vernon, Ph.D.
W. D. Wright, Ph.D.

Medical Mycology

J. T. Duncan, F.R.C.S.I., D.T.M. & H. (*Chairman*).
Professor L. P. Garrod, M.D., F.R.C.P.
Sir Archibald Gray, M.D., F.R.C.P., F.R.C.S.
P. H. Gregory, D.Sc., Ph.D.
I. Muende, M.B., B.Sc., M.R.C.P.
J. Ramsbottom, O.B.E., D.Sc.
A. H. T. Robb-Smith, M.D.
Professor M. J. Stewart, M.B., F.R.C.P.
Sydney Thomson, M.D., F.R.C.P.
S. P. Wiltshire, D.Sc.
R. St. John-Brooks, M.D. (*Secretary*).

Emergency Immunological Supplies

The late Sir John C. G. Ledingham, C.M.G., D.Sc., F.R.C.P., F.R.S. (*Chairman*).
The late F. Griffith, M.B.
N. W. Hammer, T.D., B.Sc., M.R.C.S.
Sir Percival Hartley, C.B.E., M.C., D.Sc., F.R.S.
Major-General H. Marrian Perry, C.B., O.B.E., F.R.C.P., *late* R.A.M.C. (*until September*, 1942).
Major-General L. T. Poole, D.S.O., M.C., K.H.P., *late* R.A.M.C. (*from September*, 1942).
A. Landsborough Thomson, C.B., O.B.E., D.Sc.
The late Professor W. W. C. Topley, M.D., F.R.C.P., F.R.S.
F. J. C. Herrald, M.B., M.R.C.P.E. (*Secretary*).

Blood Depots

Professor G. Payling Wright, D.M., F.R.C.P. (*Chairman*).
H. F. Brewer, M.D.
M. Maizels, M.D., F.R.C.P.
J. O. Oliver, M.B., B.S.
The late Professor W. W. C. Topley, M.D., F.R.C.P., F.R.S.
Miss Janet M. Vaughan, O.B.E., D.M., F.R.C.P.
The late D. K. M. Chalmers, M.D., D.P.H. (*Secretary*).

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Blood Transfusion Research

A. N. Drury, C.B.E., M.D., F.R.S. (*Chairman*).
H. F. Brewer, M.D.
Professor D. F. Cappell, M.D.
Flying Officer G. R. V. Coombs, M.R.C.S., L.R.C.P., R.A.F.V.R. (*from* 1943).
Professor T. B. Davie, M.D., F.R.C.P.
R. I. N. Greaves, M.D.
C. R. Harington, Ph.D., F.R.S.
Sir Percival Hartley, C.B.E., M.C., D.Sc., F.R.S.
Surgeon Commander W. A. Hopkins, O.B.E., M.D., M.R.C.P.I., R.N.
Wing Commander J. R. R. Jenkins, M.R.C.S., L.R.C.P., R.A.F. (*from* 1944).
Captain A. Kekwick, M.B., M.R.C.P., R.A.M.C. (*until May*, 1941).
R. A. Kekwick, D.Sc.
J. F. Loutit, D.M., M.R.C.P.
Flying Officer J. B. MacArthur, R.A.F.V.R. (*until* 1943).
Surgeon Lieutenant-Commander N. M. McArthur, M.D.
Flight Lieutenant J. M. McBride, M.B., Ch.B., R.A.F.V.R.
A. S. McFarlane, M.B., B.Sc.
M. Maizels, M.D., F.R.C.P.
Major W. d'A. Maycock, M.B.E., M.D., R.A.M.C.
Sir Philip Panton, M.B., B.Ch.
L. W. Proger, M.R.C.S., L.R.C.P.
Surgeon Captain S. G. Rainsford, M.D., D.P.H., R.N.
F. J. W. Roughton, Ph.D., F.R.S.
O. M. Solandt, M.D., M.R.C.P.
W. S. Stanbury, M.B.E., M.D.
C. P. Stewart, M.Sc., Ph.D.
The late G. L. Taylor, M.D., F.R.C.P.
J. W. Trevan, M.B., B.Sc., F.R.C.S., F.R.S.
Janet M. Vaughan, O.B.E., D.M., F.R.C.P.
Professor G. Payling Wright, D.M., F.R.C.P.
The late D. K. M. Chalmers, M.D., D.P.H. (*Secretary until June*, 1943).
D. P. Cuthbertson, D.Sc., M.D. (*Secretary from June*, 1943).

Additional Members of Sub-Committees

Fainting in Donors—(*Chairman :* A. N. Drury, C.B.E., M.D., F.R.S. ;
Secretary : Janet M. Vaughan, O.B.E., D.M., F.R.C.P.).
Professor A. Bradford Hill, D.Sc., Ph.D.
Lieutenant C. L. Greenbury, M.B., B.S., R.A.M.C.
Captain Faith Poles, M.B., B.S., R.A.M.C.

Reactions—(*Chairman :* A. N. Drury, C.B.E., M.D., F.R.S. ;
Secretary : Janet M. Vaughan, O.B.E., D.M., F.R.C.P.).
W. Feldberg, M.D., F.R.S.
A. A. Miles, F.R.C.P.
P. L. Mollison, M.D., M.R.C.P.

Preventive Medicine

Sir W. Wilson Jameson, K.C.B., M.D., F.R.C.P., D.P.H. (*Chairman*).
J. A. H. Brincker, M.B., D.P.H., F.R.I.C.
Sir W. Allen Daley, M.D., F.R.C.P., D.P.H.
J. Fenton, C.B.E., M.D., M.R.C.P., D.P.H.
J. Ferguson, C.B.E., M.B., D.P.H.
W. M. Frazer, O.B.E., M.D., M.Sc., D.P.H.
E. H. R. Harries, M.D., F.R.C.P., D.P.H.
Professor A. Bradford Hill, D.Sc., Ph.D.
W. D. Hood, M.B., D.P.H.
J. R. Hutchinson, M.D., D.P.H.
Professor R. A. McCance, M.D., Ph.D., F.R.C.P.
Sir Alexander S. M. MacGregor, O.B.E., M.D., D.P.H., K.H.P.
R. H. Parry, M.D., F.R.C.P., D.P.H.
Professor R. M. F. Picken, M.B., D.P.H.
Professor J. C. Spence, M.C., M.D., F.R.C.P.
The late D. K. M. Chalmers, M.D., D.P.H. (*Secretary*).

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Cross-Infection in Hospital Wards

E. H. R. Harries, M.D., F.R.C.P., D.P.H. (*Chairman*).
V. D. Allison, M.D., D.P.H.
W. H. Bradley, D.M.
W. E. Crosbie, M.B., D.P.H.
R. Cruickshank, M.D., M.R.C.P., D.P.H.
R. H. Dobbs, M.D., M.R.C.P.
W. M. Frazer, O.B.E., M.D., M.Sc., D.P.H.
J. D. McLaggan, M.B., F.R.C.S.
B. A. Peters, M.D., D.P.H.
Miss Dorothy Taylor, M.D., D.P.H.
Miss Florence E. Vine, S.R.N., S.C.M.
The late Professor Hedley D. Wright, M.D., D.Sc.
Miss Joyce Wright, D.M.
The late D. K. M. Chalmers, M.D., D.P.H. (*Secretary*).

Sterilisation of Syringes

Professor G. S. Wilson, M.D., F.R.C.P., D.P.H., K.H.P. (*Chairman*).
V. D. Allison, M.D., D.P.H.
Professor H. Berry, B.Sc., F.R.I.C., Ph.C.
Professor A. D. Gardner, D.M., F.R.C.S.
Professor L. P. Garrod, M.D., F.R.C.P.
J. E. McCartney, D.Sc., M.D.
Professor J. McIntosh, M.D., LL.D.
A. A. Miles, F.R.C.P.
H. J. Parish, M.D., F.R.C.P.E.
E. T. C. Spooner, M.D. (*Secretary*).

Hospital Morbidity Statistics

Sir Ernest Rock Carling, M.B., F.R.C.S., F.R.C.P. (*Chairman*).
Major-General Sir Alexander Biggam, K.B.E., C.B., M.D., F.R.C.P., *late* R.A.M.C.
J. Boyd, M.D., B.Sc., F.R.C.P.I.
Major C. Cassidy, M.C., M.B., R.A.M.C.
Surgeon Vice-Admiral Sir Sheldon F. Dudley, K.C.B., O.B.E., M.D., F.R.C.P., F.R.S. K.H.P.
Professor G. E. Gask, C.M.G., D.S.O., F.R.C.S.
Professor M. Greenwood, D.Sc., F.R.C.P., F.R.S.
The late J. M. McCloy, M.D., K.H.P.
P. L. McKinlay, M.D., D.P.H.
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APPENDIX F

ORDER OF THE COMMITTEE OF PRIVY COUNCIL FOR MEDICAL RESEARCH ALLOWING AMENDMENTS TO THE CHARTER OF THE MEDICAL RESEARCH COUNCIL

At the Council Chamber, Whitehall. The 1st day of November, 1943. By a Committee of the Lords of His Majesty's Most Honourable Privy Council.

WHEREAS by Article 9 of the Charter of the Medical Research Council it is provided that the said Council may, by Special Resolution in that behalf, passed at any meeting by a majority of not less than two-thirds of the Members present and voting (being an absolute majority of the whole number of the Council), and confirmed at a meeting held not less than one month and not more than three months afterwards, by a like majority, alter, amend or add to the Charter of the said Medical Research Council, and such alteration, amendment or addition shall be effectual when allowed by the Committee of the Privy Council appointed by Order in Council of the 11th day of March, 1920 (as amended by Order in Council of the 26th day of July, 1926):

AND WHEREAS certain alterations, amendments and additions to the Charter of the said Medical Research Council were allowed by an Order of the Committee of the Privy Council of the 1st day of March, 1926:

AND WHEREAS the said Medical Research Council did, on the 16th day of July, 1943, in pursuance of the said Charter by Special Resolution duly make further alterations, amendments and additions to the said Charter, which said Special Resolution was duly confirmed by the said Council on the 24th day of September, 1943:

AND WHEREAS the said further alterations, amendments and additions have been submitted to the Committee of the Privy Council for allowance:

NOW, THEREFORE, Their Lordships having taken the said further alterations, amendments and additions to the said Charter (a copy whereof is hereunto annexed) into consideration, are pleased to allow the same.

E. C. E. Leadbitter.

FURTHER ALTERATIONS, AMENDMENTS AND ADDITIONS to the CHARTER OF THE MEDICAL RESEARCH COUNCIL referred to in the foregoing ORDER.

Article 2. (i)—*Delete* " (i)."

Delete " 31st day of January, 1926," and *substitute* " 30th day of September, 1943."

Delete " eleven " and *substitute* " twelve."

Article 2. (ii)—*Delete* " 2. (ii) " and *substitute* " 3."

Delete " eight " and *substitute* " nine."

Article 3. —*Delete* Articles 3. and 4. and *substitute* the following:

" 4. On the 30th day of September, 1944, and thereafter at intervals of one year every member of the Medical Research Council who has served for four years or longer since the date of his last appointment as such shall retire, and no member appointed in respect of his scientific qualifications retiring as aforesaid shall be eligible for re-appointment until a period of at least one year has elapsed since the date of his last retirement."

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The investigations mentioned in the text of the Report are there grouped under administrative headings—depending, for instance, on whether the work formed part of the programme of one of the Council's expert committees or whether it was done at the National Institute for Medical Research, by members of the Council's staff elsewhere, or by the recipients of grants in hospitals and universities. It thus happens that cognate researches may be described in widely separated sections. The following cross-classification by scientific subjects is accordingly given, reference to the same work being made under more than one title when it is of interest from different points of view. This may be found to serve a wider purpose than a detailed alphabetical index to items of investigation.

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